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(54) **INTERMEDIATES FOR THE SYNTHESIS OF EPOTHILONES AND METHODS FOR THEIR
PREPARATION**

**ZWISCHENPRODUKTE IN DER SYNTHESE VON EPOTHILONEN UND VERFAHREN ZU DEREN
HERSTELLUNG**

**INTERMEDIAIRES POUR LA SYNTHESE D'EPOTHILONES ET PROCEDE DE PREPARATION
DESDITS INTERMEDIAIRES**

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- **K.C.NICOLAOU ET AL: "Total syntheses of
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Description

Summary of the Invention

[0001] The invention relates to a method of synthesis of an intermediate useful for the synthesis of epothilone B and desoxyepothilone B and derivatives thereof, as well as to certain partial reaction sequences for the production of key intermediates.

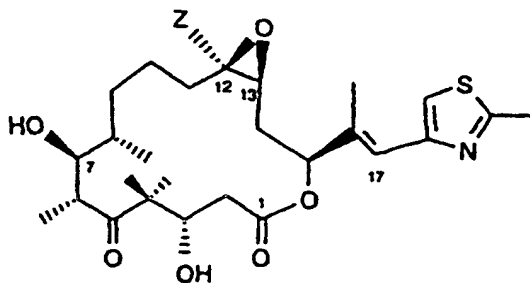
Background of the Invention

[0002] Among cytotoxic agents for the treatment of tumors, Taxol® (Paclitaxel), a microtubule stabilizing agent, has become a very important compound with a remarkable economic success (see McGuire, W.P., et al., Ann. Int. Med. 111, 273-9 (1989)).

[0003] Taxol® has a number of disadvantages. Especially its extremely low solubility in water represents a severe problem. It has become necessary to administer Taxol in a formulation with Cremophor EL® (polyoxyethylated castor oil; BASF, Ludwigshafen, Germany) which has severe side effects, causing inter alia allergic reactions that in one case even were reported to have led to the death of a patient. More severely, certain tumor types are known to be refractory against treatment with Taxol®.

[0004] Taxol® treatment is associated with a number of significant side effects and some major classes of solid tumors, namely colon and prostate, are poorly responsive to this compound (see Rowinsky E.K., loc. cit.).

[0005] The epothilones A and B are a new class of microtubule stabilizing cytotoxic agents (see Gerth, K. et al., J. Antibiot. 49, 560-3 (1966); Hoefle et al., DE 41 38 042) of the formulae:



wherein Z is hydrogen (epothilone A) or methyl (epothilone B).

[0006] These compounds have the following advantages:

- (i) they show better water solubility than Taxol and are thus more appropriate for formulation; and
- (ii) they have been reported to be active also against the proliferation of cells that, due to the activity of the P-glycoprotein efflux pump which renders them multidrug resistant, show resistance to the treatment with other chemotherapeutics, e.g. Taxol (see Bollag, D. M., et al., "Epothilones, a new class of microtubule-stabilizing agents with a Taxol-like mechanism of action", Cancer Research 55, 2325-33 (1995); and Bollag D.M., Exp. Opin. Invest. Drugs 6, 867-73 (1997); and
- (iii) despite apparently sharing the same, or at least a largely overlapping binding site on the microtubule, the epothilones have been shown to be active against a Taxol®-resistant ovarian carcinoma cell line with an altered β -tubulin (see Kowalski, R. J., et al., J. Biol. Chem. 272(4), 2534-2541 (1997)).

[0007] Due to their impressive biological profile, multiple initial efforts towards the synthesis of epothilones appeared almost simultaneously in the literature. Three groups described total syntheses of epothilone A, and two total syntheses of epothilone B appeared concurrently as well. In addition, a flood of papers appeared which presented partial solutions towards the synthesis of epothilones. Since these studies, many derivatives have been synthesized and their biological profiles have been tested.

[0008] Especially epothilone B provides important biological properties that are exemplary for other epothilones:

Epothilone B is appropriate preferably in the treatment of proliferative diseases, such as of gastrointestinal tumors, more preferably (1) a tumor of the colon and/or the rectum (colorectal tumor), especially if it is refractory to a (meaning at least one) representative of the taxane class of anti-cancer agents, in particular paclitaxel, and/or at

least one standard treatment with an other chemotherapeutic, especially 5-fluorouracil; (2) a tumor of the genitourinary tract, more preferably a tumor of the prostate, including primary and metastatic tumors, especially if refractory to hormone treatment ("hormone refractory prostate cancer") and/or treatment with other standard chemotherapeutics; (3) an epidermoid tumor, more preferably an epidermoid head and neck tumor, most preferably a mouth tumor; (4) a lung tumor, more preferably a non-small cell lung tumor, especially any of these tumors that is refractory to treatment with one or more other chemotherapeutics (especially due to multidrug resistance), especially to treatment with a member of the taxane class of anti-cancer agents, in particular TAXOL®; or (5) a breast tumor, more preferably one that is multidrug resistant, especially refractory to treatment with a member of the taxane class of anti-cancer agents, in particular TAXOL®; relating especially also to the treatment of a multidrug resistant lung tumor (preferably a non-small cell lung tumor), a multidrug resistant breast tumor, or a multidrug resistant epidermoid tumor, or in a broader sense of the invention to a treatment schedule for the treatment of an aforementioned or (in a broader sense of the invention) any other tumor.

Epothilone B is preferably used weekly or three-weekly; preferably for weekly treatment the dose is between about 0.1 and about 6, preferably about 0.1 and about 5 mg/m², more preferably about 0.1 and about 3 mg/m², even more preferably 0.1 and 1.7 mg/m², most preferably about 0.3 and about 1 mg/m²; for three-weekly treatment (treatment every three weeks or every third week) the dose is between about 0.3 and about 18 mg/m², preferably about 0.3 and about 15 mg/m², more preferably about 0.3 and about 12 mg/m², even more preferably about 0.3 and about 7.5 mg/m², still more preferably about 0.3 and about 5 mg/m², most preferably about 1.0 and about 3.0 mg/m². This dose is preferably administered to the human by intravenous (i.v.) administration during 2 to 180 min, preferably 2 to 120 min, more preferably during about 5 to about 30 min, most preferably during about 10 to about 30 min, e.g. during about 30 min.

[0009] Preferably, especially in the case of weekly treatment, rest periods of more than one week, more preferably of two to ten weeks, more preferably three to six weeks after the preceding treatment may be necessary after for example 3, 4, 6, 8, or more treatment cycles, depending on patient condition, to allow for sufficient recovery from the preceding treatment.

[0010] The pharmaceutical compositions comprise from about 0.00002 to about 95%, especially (e.g. in the case of infusion dilutions that are ready for use) of 0.0001 to 0.02%, or (for example in case of infusion concentrates) from about 0.1% to about 95%, preferably from about 20% to about 90%, active ingredient (weight by weight, in each case). Pharmaceutical compositions according to the invention may be, for example, in unit dose form, such as in the form of ampoules, vials, suppositories, dragées, tablets or capsules.

[0011] Preferred is an infusion formulation comprising epothilone B and a pharmaceutically acceptable organic solvent. The pharmaceutically acceptable organic solvent used in a formulation according to the invention may be chosen from any such organic solvent known in the art. Preferably the solvent is selected from alcohol, e.g. absolute ethanol or ethanol/water mixtures, more preferably 70% ethanol, polyethylene glycol 300, polyethylene glycol 400, polypropylene glycol or N-methylpyrrolidone, most preferably polypropylene glycol or 70% ethanol or especially polyethylene glycol 300.

[0012] Epothilone B may preferably be present in the formulation in a concentration of about 0.1 to about 100 mg/ml, more preferably about 1 to about 100 mg/ml, still more preferably about 1 to about 10 mg/ml (especially in infusion concentrates).

[0013] It is a goal of the present invention to provide novel routes to manufacture an intermediate for the synthesis of epothilone B and its predecessor, desoxyepothilone B.

[0014] In contrast to a published synthesis by Nicolaou et al. (see J. Am. Chem. Soc. 119, 7974-91 (1997)) for the synthesis of epothilone B, the new route is more convergent, that is, it is based on three rather than two key fragments that have to be assembled to the final product. The disadvantage of the prior art two-fragment strategy consists in the fact that many more steps are required to prepare the individual fragment. Therefore the new synthesis offers large advantages.

Detailed Description of the invention

[0015] The invention relates to a formal total synthesis route via an intermediate appropriate for the synthesis of epothilone B and analogues thereof. The approach uses macrolactonization for the final ring closure and provides an especially convergent strategy to obtain the key building blocks.

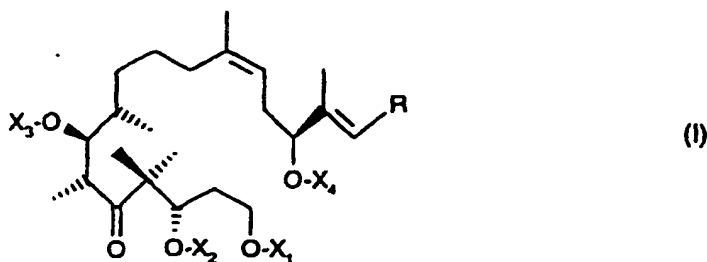
[0016] The invention also especially relates to the synthesis of the aldehyde 17 and the aldehyde 18 (see reaction scheme 2) starting from (+)-malic acid, which is largely unrelated to published synthesis of these compounds and is much more practical.

[0017] The invention also especially relates to processes of manufacture for ethyl ketone 30, either via the ester 26

(scheme 4) or acyl suitam **31**. The latter compound has been described in the literature (see Synlett (1997), 623). However, if the procedure recommended in that publication is followed, the wrong (namely the 3R-) enantiomer is obtained instead of the desired isomer **31**, which is required for the synthesis of epothilones.

[0018] The invention also especially relates to the synthesis of **19** via a Pd-catalyzed coupling reaction, which offers the large advantage of highly selective formation of a cis-bond at the double bond connecting carbon atoms 12 and 13 in epothilone B as well as to the intermediate **19**. This compound has not been described previously as a homogeneous double bond isomer at the C12-C13 double bond of epothilone B. Surprisingly, the above reaction is stereoselective only for the methyl substituent Z found in the formula of epothilone B given in the introduction.

[0019] The invention relates especially to a method for the synthesis of an intermediate of the formula I



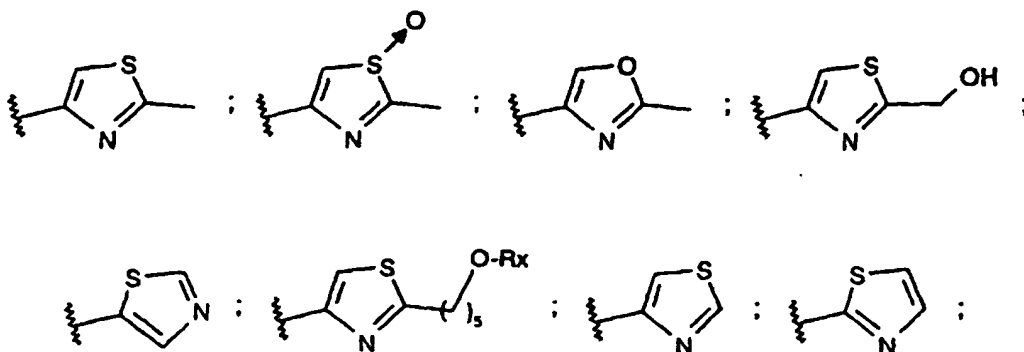
wherein R is a heterocyclyl moiety and X₁, X₂, X₃ and X₄ are, independently of each other, protecting groups.

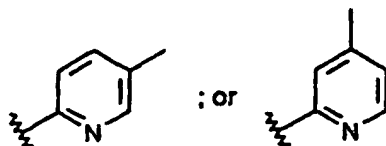
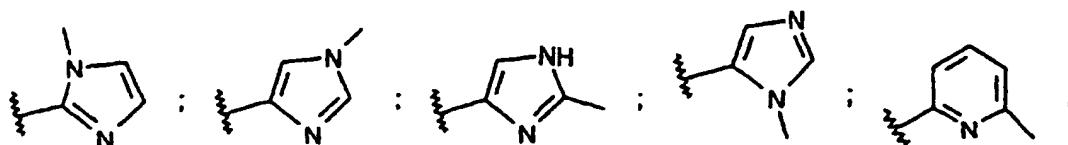
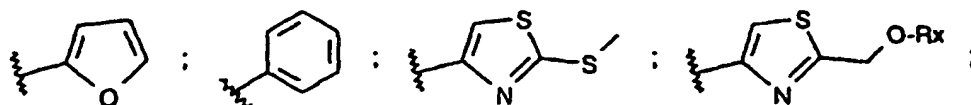
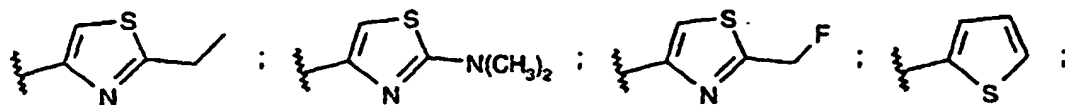
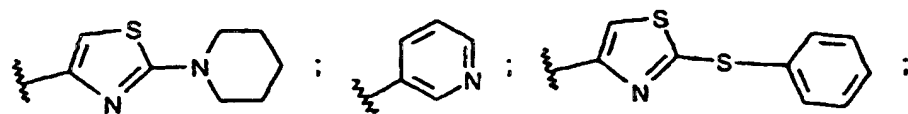
[0020] The intermediate of the formula I can then be used for the synthesis of epothilone B and analogues thereof via various steps including macrolactonization and epoxidation, using methods known in the art, see especially Nicolaou et al., J. Am. Chem. Soc. **119**, 7974-91 (1997). If the epoxidation step is omitted (and, if present, protecting groups are cleaved of), desoxyepothilone B, the analogue of epothilone B where instead of the oxirane ring a double bond is present, can be synthesized.

[0021] Within the present disclosure, the general definitions used hereinbefore and hereinafter preferably have the following meaning, if not indicated otherwise:

[0022] A heterocyclyl moiety R is preferably a monocyclic moiety with 5 or 6 ring atoms, wherein 1 to 3, especially one or two, ring carbon atoms each are replaced by a heteroatom selected from nitrogen, oxygen or sulfur; the heterocyclic moiety may be unsubstituted or substituted by one or more substituents that are preferably independently selected from the group consisting of oxo, lower alkyl, especially methyl, hydroxy-lower alkyl, especially hydroxymethyl, lower alkylmercapto, especially methylmercapto, phenylmercapto, amino, mono- or di-lower alkylamino, especially dimethylamino, halogen-lower alkyl, such as fluoromethyl, or acyloxy-lower alkyl, such as lower alkanoyloxy-lower alkyl, e.g. 5-acetyloxy-pentyl or acetyloxymethyl.

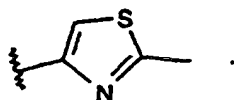
[0023] Most preferably, the heterocyclyl moiety has any one of the following formulae:





30 wherein Rx is acyl, especially lower alkanoyl, such as acetyl;

[0024] Most preferably, the moiety R has the formula



40 [0025] A protecting group is especially selected from the group comprising a silyl protecting group, especially diaryl-lower alkyl-silyl, such as diphenyl-*tert*-butylsilyl, or more preferably tri-lower alkylsilyl, such as *tert*-butyldimethylsilyl or trimethylsilyl; lower alkanoyl, such as acetyl; benzoyl; lower alkoxy-carbonyl, such as *tert*-butoxycarbonyl; tetrahydro-pyranyl; phenyl-lower alkoxy-carbonyl, such as benzyloxycarbonyl; and unsubstituted or substituted 1-phenyl-lower alkyl, such as benzyl or *p*-methoxybenzyl.

45 [0026] The protecting groups may be present in any precursors and intermediates and should protect the functional groups concerned against unwanted secondary reactions, such as acylations, etherifications, esterifications, oxidations, solvolysis, and similar reactions. In certain cases, the protecting groups may, in addition to this protection, effect a selective, typically stereoselective, course of reactions. It is a characteristic of protecting groups that they lend themselves readily, i.e. without undesired secondary reactions, to removal, typically by solvolysis, reduction, photolysis or also by enzyme activity, for example under conditions analogous to physiological conditions, and that they are not present in the end-products. The specialist knows, or can easily establish, which protecting groups are suitable with

the reactions mentioned hereinabove and hereinafter.

[0027] The protection of functional groups by such protecting groups, the protecting groups themselves, and their cleavage reactions are described for example in standard reference works, such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York 1981, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981, in "Methoden der organischen Chemie" (*Methods of organic chemistry*), Houben Weyl, 4th edition, Volume 15/I, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jeschkeit, "Aminosäuren, Peptide, Proteine" (*Amino acids, peptides, proteins*), Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (*Chemistry of carbohydrates: monosaccharides and derivatives*), Georg Thieme Verlag, Stuttgart 1974.

[0028] The prefix "lower" means that the respective moiety preferably has up to and including a maximum of 7 carbon atoms, more preferably up to 4 carbon atoms.

[0029] Lower alkyl can be linear or branched and is especially methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl.

[0030] Halogen is preferably fluorine, chlorine, bromine or iodine.

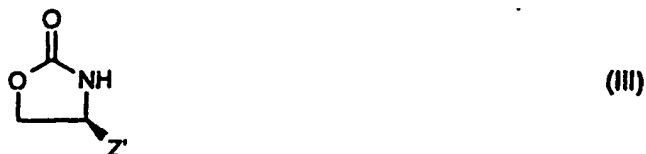
[0031] The process steps making up the process of the invention and the preferred aspects thereof can be described preferably as follows:

Hereinbefore and hereinafter, the definitions of the moieties R, X₁, X₂, X₃ and X₄ have the meaning given under formula I, if not indicated otherwise. A moiety X, where mentioned, stands for a protecting group as defined above (and may, depending on the exact position, correspond to any of X₁, X₂, X₃ and X₄ if appropriate).

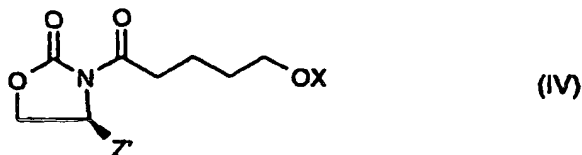
[0032] The reaction sequence starts with a compound of the formula II



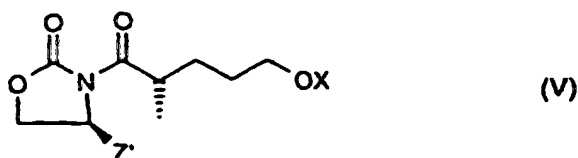
wherein Y is the radical of an organic or inorganic acid devoid of its dissociable hydrogen, e.g. halogen, especially chlorine, and X is a protecting group as described above, especially benzyl; which is reacted with an oxazolidone of the formula III



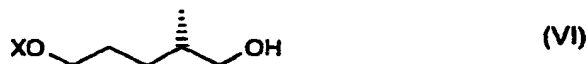
wherein Z' is lower alkyl, e.g. isopropyl, or preferably phenyl-lower alkyl, especially benzyl, in an appropriate solvent, e.g. tetrahydrofuran, in the presence of a strong base, especially methyl magnesium bromide, and then of an appropriate tertiary amino base, such as 4-dimethylaminopyridine; or preferably of an alkalimetal alkylid, such as n-butyllithium; at low temperatures, e.g. in the range from -80 to + 10 °C, yielding a compound of the formula IV,



wherein X and Z' have the meanings given above; (IV) is then C-methylated, e.g. with a halomethane, especially methyl iodide, in the presence of a strong base, e.g. sodium hexamethyldisilazide, to yield a compound of the formula V,



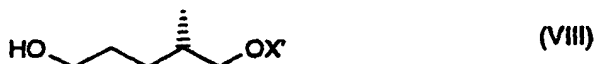
10 wherein X and Z' are defined as above; from that compound, then a compound of the formula VI,



15 wherein X is as given above is set free by reductive cleavage, e.g. by reaction with a complex hydride, such as lithium aluminium hydride; then, a protecting group X' selected from the protecting groups mentioned above for X₁ to X₄, but different from X in formula VI, preferably tert-butyl-dimethylsilyl, is introduced at the free hydroxy group that allows that the protecting group X in the compound of formula VI can be cleaved off without affecting the newly introduced protecting group, e.g. by reaction with an alkylsilylhalogenide, such as tert-butyl-dimethylsilyl chloride, to yield a bis-protected compound of the formula VII,



30 with X and X' as described above; from this compound, then the protecting group X, preferably benzyl, is cleaved off under appropriate conditions, e.g. by catalytic transfer hydrogenolysis, reaction with lithium 4,4'-di-tert-butyl-biphenyl or by catalytic hydrogenation, to yield a compound of the formula VIII,



40 with X' as defined for the compound of the formula VII; that compound VIII is then reacted with a halogenide of an organic sulfonic acid to yield the corresponding sulfonic acid ester of the formula IX,



45 wherein Q is organic sulfonyl, especially alkanesulfonyl, such as methanesulfonyl, and that sulfonyl ester is then reacted with a metal iodide, especially sodium iodide, to yield the corresponding iodide compound of the formula X,



with X' as defined above.

[0033] This is the synthesis of one of the three intermediates for the convergent synthesis.

55 [0034] Independently from that sequence of reactions,

a) a compound of the formula XI,



wherein R is as described under formula I and Hal is halogen, especially chlorine, is reacted with a tri-alkyl phosphite, especially triethyl phosphite, to yield a phosphonate compound of the formula XII,



wherein R is as defined under formula I and each of A is alkyl, especially ethyl.

[0035] Independently, (5S)-(2,2-cyclohexylidene)-4-oxo-1,3-dioxolane (synthesized starting from L-(-)-malic acid, see Hanessian et al., J. Orgn. Chem. 58, 7768-81 (1993)) is reacted with $\text{BH}_3\text{-Me}_2\text{S}$ complex and B $(\text{OCH}_3)_3$ and methanol to yield 3(S)-dihydro-3-hydroxy-2(3H)-furanone (compound 11 in reaction scheme 2 below); that is then protected by introduction of a protecting group X_4 , especially using a lower alkylsilyl halogenide, such as tert-butyldimethylsilylchloride, to yield a compound of the formula XIII,



wherein X_4 is a protecting group, especially tert-butyldimethylsilyl; the compound of formula XIII is then reacted with an methyl metal or methyl metal derivative, especially methyl lithium, to the compound of the formula XIV,



wherein X_4 is as defined under formula XIII; the compound of formula XIV is reacted with a further reagent capable of introducing a protecting group, especially an alkylsilyl halogenide, such as tert-butyldimethylsilyl chloride, yielding a compound of the formula XV,



wherein X and X_4 are a protecting group, especially tert-butyldimethylsilyl, which compound is then reacted with a phosphonate compound of the formula XII given above in the presence of a strong base, especially n-butyl lithium, yielding a compound of the formula XVII,



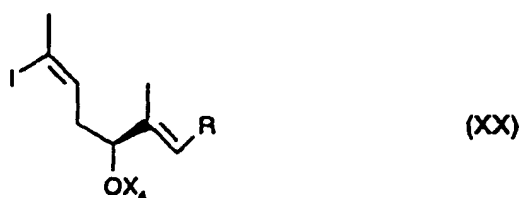
10 wherein X and X₄ are as defined under formula XIII and R is as defined under formula I; the compound of the formula XVII is then deprotected partially under appropriate conditions (e.g., if X is tert-butyl(dimethyl)silyl, by using aqueous hydrofluoric acid) to give a compound of the formula XVIII,



20 wherein the moieties X₄ and R are as defined under formula XVII; the compound of the formula XVIII is oxidized selectively, e.g. using dimethylsulfoxide and oxalylchloride in dichloromethane, to the corresponding aldehyde of the formula XIX,



30 wherein R and X₄ are as defined under formula XVII, which is then, by reaction with a strong base, especially n-butyl lithium, and iodine in the presence of triphenylphosphonium iodide (either with isolation of the iodoethyl phosphonium iodide or in a one pot synthesis), and subsequent addition of a different or the same base as above, especially sodium hexamethyldisilazide, converted into a compound of the formula XX,



45 (this reaction being highly specific in yielding mainly or purely the cis-compound wherein R and X₄ are as defined under formula XVII.

50 [0036] This reaction sequence is allowing for the introduction of a large variety of heterocyclic moieties R and thus providing an important new way of synthesizing analogs of epothilone B and desoxyepothilone B wherein R has one of the other meanings than 2-methylthiazolyl given above under formula (I)

[0037] The sequence of reactions from XIII to XV, especially the reaction from XIII to XIV and the reaction from XIV to XV, as well as the whole sequence leading from L-malic acid to XX (as described in the examples), are new and form a special part of the invention.

55 [0038] The compounds of the formulae XIV (especially compound 13 in scheme 2), XVII (if R is other than 2-methylthiazol-4-yl and X₄ is other than tert-butyl(dimethyl)silyl) (especially 15 in scheme 2), XVIII (if R is other than 2-methylthiazol-4-yl and X₄ is other than tert-butyl(dimethyl)silyl) (especially 16 in scheme 2), the compound of formula XX if R is other than 2-methylthiazol-4-yl, and compound 18 in scheme 2, are new and are also part of the invention.

[0039] The compound of the formula XX is the second of the three intermediates for the convergent synthesis.

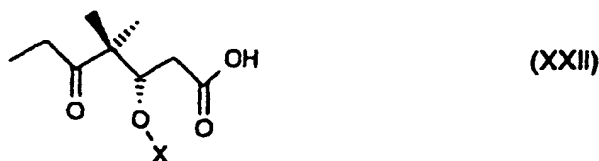
[0040] The third intermediate for the convergent synthesis is manufactured preferably by one of the two ways (a) and (b) described hereinafter:

(a) (see also scheme 4) Diethylketon is reacted in the presence of zinc dust (activated, e.g. with 1,2-dibromoethane) in the presence of $B(OCH_3)_3$ with ethyl 2-bromo-2-methylpropanoate (Fluka, Buchs, Schweiz) to ethyl 2,2-dimethyl-3-ethyl-3-hydroxypentanoate 22, which is then reacted with a dehydrating agent, especially phosphorus pentoxide, to ethyl (E)-2,2-dimethyl-2-ethyl-3-pentenoate 23; which is then reacted in the presence of an appropriate complex hydride, e.g. lithium aluminium hydride, to E-2,2-dimethyl-3-ethyl-3-penten-1-ol 24; this is then oxidised with an appropriate oxidant, e.g. dimethylsulfoxide in dichloromethane and oxalyl chloride, to (E)-2,2-dimethyl-3-ethyl-3-pentenal 25, which is then reacted with (S)-(-)-2-hydroxy-1,2,2-triphenyl acetate (FLUKA) in the presence of a strong base, e.g. Li-diisopropylamide, to (1S)-2,2,1-triphenyl-2-hydroxyethyl-(3S, E)-4,4-dimethyl-5-ethyl-3-hydroxy-5-heptenoate 26; that compound is transformed, by reaction with an appropriate complex hydride, e.g. lithium aluminium hydride, into (S)-(E)-4,4-dimethyl-5-ethyl-5-heptene-1,3-diol 28, which is then converted, by reaction with acetone in the presence of anhydrous copper sulfate, a strong organic acid, e.g. p-toluene sulfonic acid, and a tertiary nitrogen base, e.g. pyridine, to give (S)-(E)-2,2-dimethyl-[1,3]dioxan-4-yl)-3-ethyl-2-methyl-pent-3-ene 29; this compound is then converted to the third intermediate for the convergent synthesis, the ethyl ketone (S)-2-(2,2-dimethyl-[1,3]dioxan-4-yl)-2-methyl-pentan-3-one 30 by ozonolysis.

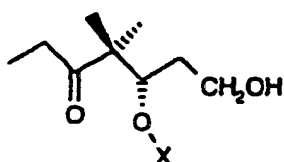
(b) (see scheme 3) Alternatively, 30 can be obtained advantageously by reaction of (2R)-N-acetylbornane-10,2-sultam (see Tetrahedron Lett. 33, 2439 (1992)) in the presence of a dialkylborane triflate or dialkylborane chloride, especially diethylborane triflate (which can, but does not have to be, generated in situ from triethylborane and CF_3SO_3H) and after addition of a tertiary nitrogen base, e.g. diisopropylethyl amine, with 2,2-dimethyl-3-oxo-pentanal (see J. Am. Chem. Soc. 119, 7974 (1997)) that leads to the sultam product 31, which is then reacted, in the presence of a tertiary nitrogen base, such as 2,6-lutidine, with a reagent appropriate for the introduction of a protecting group, e.g. an alkylsilylhalogenide, especially tert-butyldimethylsilyl-triflate, to give a compound of the formula XXI



wherein X is a protecting group, especially tert-butyldimethylsilyl (especially compound 32); the compound of formula XXI is then converted into the corresponding free acid of the formula XXII by reaction with an appropriate aqueous base, e.g. LiOH, NaOH, KOH, or LiOOH, especially with LiOOH



wherein X is as defined under formula XXI (especially compound 33); the compound of formula XXII is then reduced to the corresponding alcohol of the formula XXIII

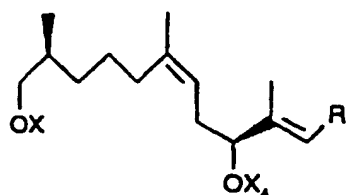


(XXIII)

wherein X is as defined under formula XXI (especially compound 34), by reaction eg. with Borane/dimethylsulfide, and finally that compound is deprotected and transformed into compound 30 by reaction in acetone/acid, such as acetone/trifluoroacetic acid.

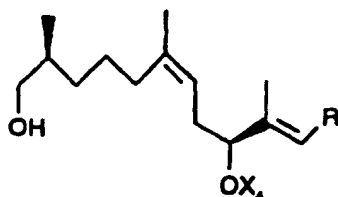
[0041] Thus, the third intermediate for the convergent synthesis of the compound of the formula I is prepared.

[0042] In a next step, first the two intermediates of the formulae X and XX (preferably compounds 8 and 18 in scheme 5) are coupled by reaction of the compound of the formula X with a suspension of powdered Zn/Cu couple in the presence of an activator, e.g. 1,2-dibromoethane, in the presence of halotrialkylsilane, such as chlorotrimethylsilane (if necessary with addition of trifluoromethanesulfonate and catalytic amounts of mercury(II) acetate to complete the first part of the reaction, and then addition of XX and a Pd(0)-complex yielding a compound of the formula XXIV,



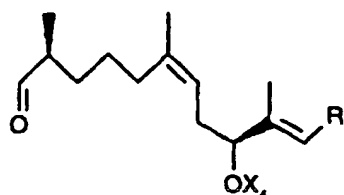
(XXIV)

wherein X and X₄ each are a protecting group, especially tert-butyldimethylsilyl, and R is as defined under formula I; the advantage of this coupling is that it yields the cis-isomer of the compound of the formula XXIV in high yield and stereospecificity the compound of the formula XXIV is then selectively deprotected, e.g. (in the case of X = alkylsilyl, especially tert-butyl-dimethylsilyl) by campher sulfonic acid, to give a compound of the formula XXV,



(XXV)

wherein X₄ and R are as defined under formula XXIV; the compound of the formula XXV is then oxidized with an appropriate oxidant, e.g. Dess-Martin periodinane, to the corresponding aldehyde of the formula XXVI

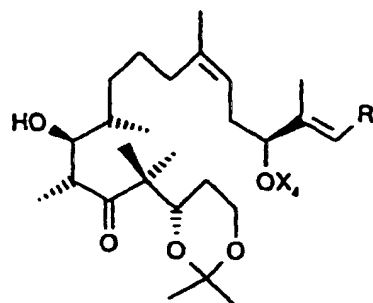


(XXVI)

wherein X₄ and R are as defined under formula XXIV.

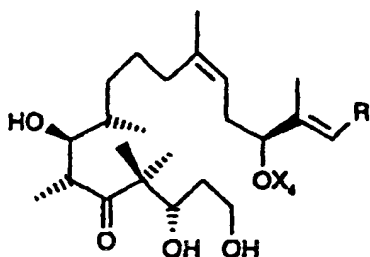
[0043] The compounds of the formulae XXIV and XXV in essentially isomeric pure cis-form, especially if R is other than 2-methylthiazolyl) are new and also part of the invention, as well as the coupling reaction of the compounds of the formulae X and XX to the compound of the formula XXIV.

[0044] The third intermediate of the convergent synthesis, compound **30**, is then reacted with the compound of the formula XXVI (preferably compound **21**) in an Aldol reaction, preferably by reaction in the presence of lithium diisopropylamide (LDA) that is first reacted with compound **30**, followed by addition of the compound of the formula XXVI, resulting in a compound of the formula XXVII,



(XXVII)

wherein X_4 and R are as defined under formula I; the compound of the formula XXVII is then deprotected under removal of the acetal moiety, e.g. using pyridinium-p-toluenesulfonate, yielding a compound of the formula XXVIII,



(XXVIII)

wherein X_4 and R are as defined under formula I; finally, the compound of the formula I is obtained by introduction of protecting groups X_1 , X_2 and X_3 with appropriate reagents, e.g. alkylsilyl halogenides or alkylsilyl trifluoromethanesulfonates, especially tert-butyl-dimethylsilyltrifluoromethanesulfonate, in the presence of an appropriate tertiary nitrogen base, such as 2,6-lutidine.

[0045] The compound of the formula XXIV, especially where R is other than 2-methylthiazol-4-yl, is also part of the invention.

[0046] All reactions are done in appropriate solvents, at appropriate temperatures and, if necessary, under an inert gas, such as argon or nitrogen.

[0047] The skilled person will understand that the reaction conditions given above can be replaced by analogous reaction conditions that are in principle known in the art. In addition, the skilled person will be able to select the appropriate specific reaction conditions for the reaction steps given hereinbelow and hereinafter where reactions are described generally herein.

[0048] The reactions given above are preferably carried out under conditions analogous to those given in the Examples.

[0049] The invention relates most especially to the above reaction sequences where the respective intermediates and educts mentioned in the examples are used instead of the general formulae II to presented above.

[0050] The starting materials are known, can be synthesized according to known procedures, are available commercially or can be synthesized in analogy to the materials given below in the examples.

Examples

[0051] The following examples are intended to illustrate the invention.

[0052] Temperatures are given in degrees Celsius ($^{\circ}\text{C}$). The abbreviations used have the following meanings:

h	hour(s)
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(continued)

min	minute(s)
m.p.	melting point
MW	molecular weight
MS	Mass Spectroscopy
NaHMDS	sodium hexamethyldisilazide
NMR	Nuclear Magnetic Resonance
OTBDMS	tert-butyl-dimethylsilyloxy
Pd(PPh ₃) ₄	Palladium-tetrakis-(triphenylphosphin)
PPTS	pyridinium-p-toluenesulfonate
r.t.	room temperature
TBDMSO	tert-butyl-dimethylsilyloxy
THF	tetrahydrofuran
tic	thin layer chromatography (Polygram SIL G/UV, Macherey & Nagel, Düren, FRG)

[0053] Where physical data are not provided, the respective compound is used directly in the subsequent reaction step.

[0054] Flash chromatography is performed on silica gel columns (Kieselgel 60 (0.035-0.07 mm), Fluka, Buchs, Schweiz)

1) "C5" fragment (Scheme 1)

a) 5-Benzyloxypentanoyl Chloride **1**

[0055] Oxalyl chloride (1.49 ml, 17.06 mmol, 1.5 equiv) is added dropwise under nitrogen atmosphere to a solution of 2,368 g (11.37 mmol) 5-benzyloxypentanoic acid [L Börjesson et al., J. Org. Chem. **60**, 2989 - 2999 (1995)] in 15 ml of CH₂Cl₂. The mixture is stirred for 90 min at r. t. and 15 min at 40 °C. Removal of the solvent *in vacuo* gives 2.425 g (94%) of 5-benzyl-oxypentanoyl chloride **1** as a colourless oil. ¹³C-NMR (100 MHz, COCl₂): δ = 171.3; 137.4; 128.7; 128.5; 128.3; 69.4; 46.2; 29.8; 22.3; 19.1

b) (S)-3-(5-Benzyloxy-1-oxopentyl)-4-(methylethyl)-2-oxazolidinone **2a** (Z = isopropyl in Scheme 1)

[0056] 9.6 ml (28.8 mmol, 1.2 eq) of a solution of methyl magnesium bromide (3.0 M in THF) are added dropwise to a solution of (S)-4-methylethyl-2-oxazolidinone (3.100 g, 24.0 mmol) in THF (60 ml) at 0 °C within 15 min. The mixture is stirred for 15 min at 0 °C. 4-Dimethylaminopyridine (59 mg, 0.48 mmol, 0.02 equiv) is added and the mixture is cooled to -78 °C. A solution of 5-benzyl-oxypentanoyl chloride **1** (6.625 g, 29.22 mmol, 1.22 eq) in THF (20 ml) is added slowly within 30 min. The mixture is stirred for 15 min at -78 °C and then for 30 min at 0 °C. Saturated aqueous NH₄Cl solution (40 ml) is added with stirring. The organic phase is separated and the aqueous layer is extracted with diethyl ether (3 x 100 ml). The combined organic extracts are dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 2:1) affords (S)-3-(5-benzyloxy-1-oxopentyl)-4-(methylethyl)-2-oxazolidinone **2** (5.602 g, 73%) as a colourless oil which crystallizes upon standing in the cold. Recrystallization from pentane / diethyl ether yields colourless crystals, m. p. 133 °C. ¹³C-NMR (100 MHz, CDCl₃): δ = 173.0; 154.0; 138.5; 128.3; 127.6; 127.4; 72.8; 69.9; 63.3; 58.3; 35.2; 29.0; 28.3; 21.1; 17.9; 14.6

c) 3-(5-Benzyloxy-2S-methyl-1-oxopentyl)-4S-(methylethyl)-2-oxazolidinone **3a** (Z= isopropyl in Scheme 1)

[0057] To 10.1 ml (10.1 mmol, 1.1 equiv) of a solution of sodium hexamethyldisilazide (NaHMDS, 1.0 M in THF) is added a solution of (S)-3-(5-benzyloxy-1-oxopentyl)-4-(methylethyl)-2-oxazolidinone **2** (2.928 g, 9.17 mmol) in 10 ml of THF dropwise at -78 °C. The mixture is stirred for 1 h at -78 °C. A solution of iodomethane (2.9 ml) in 12.0 ml of THF is added dropwise. The mixture is stirred for 8 h at -78 °C. Saturated aqueous NH₄Cl solution (40 ml) is added with stirring. The organic phase is separated and the aqueous layer is extracted with diethyl ether (3 x 100 ml). The combined organic extracts are dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue (ratio of the diastereomeric alkylation products about 10:1) by flash column chromatography (pentane / diethyl ether 2:1) affords 3-(5-benzyloxy-2S-methyl-1-oxopentyl)-4S-(methylethyl)-2-oxazolidinone **3** (2.142 g, 70%) as a colourless oil (3 : 1 mixture of **3a** and its 2R diastereomer). ¹³C-NMR (100 MHz, CDCl₃): δ = 176.9; 153.6; 138.5; 128.3; 127.5;

127.4; 72.8; 70.2; 63.1; 58.4; 37.5; 29.7; 28.4; 27.4; 18.0; 17.9; 14.6

d) (S)-5-Benzyloxy-2-methyl-pentan-1-ol 4

[0058] Lithium aluminium hydride (235 mg, 6.19 mmol, 1.0 equiv) is added portionwise within 45 min at 0 °C to a solution of 2.064 g (6.19 mmol) of 3-(5-benzyloxy-2S-methyl-1-oxopentyl)-4S-(methylethyl)-2-oxazolidinone **3** in 35 ml of absolute diethyl ether. The mixture is stirred at 0 °C for 15 min and analyzed by tic. If starting material can still be detected, lithium aluminium hydride addition is continued until completion of the reaction. 235 µl of water, 235 µl of aqueous sodium hydroxide solution (15%) and 610 µl of water are subsequently added to the reaction mixture (or the volumes corresponding to the amount of lithium aluminium hydride added, respectively). The mixture is stirred until the precipitation of a white solid is complete and filtered through a small plug of celite. The filtrate is concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 1:1) affords (S)-5-benzyloxy-2-methyl-pentan-1-ol **4** (1.160 g, 90%) as a colourless oil. ¹³C-NMR (100 MHz, CDCl₃): δ = 138.5; 128.3; 127.6; 127.5; 72.9; 70.6; 68.1; 35.5; 29.5; 27.1; 16.5

[0059] [Alternatively (using Z = benzyl in reaction scheme 1), **4** can be synthesized as follows:

b*) 4(S)-(Benzyl)-3-(5-benzyloxy-1-oxopentyl)-2-oxazolidinone 2a (Z = isopropyl in Scheme 1)

[0060] To a solution of 2.03 g of 4-(S)-benzyl-oxazolidin-2-one in 30 ml of THF, 7.23 ml of a 1.6 M solution of n-BuLi in hexane at -78° are added over a period of 10 min. To this solution then 2.86 g of 5-benzyloxypentanoyl chloride **1** are added at the same temperature and the mixture is stirred at -78° for 30 min. After that time the reaction is quenched by the addition of 10 ml of saturated aqueous NH₄Cl, the THF is removed by evaporation, the residue is diluted with dichloromethane/water and the organic layer is separated off. The aqueous solution is extracted three times with 30 ml of dichloromethane, respectively, and the combined organic extracts are washed with 50 ml of 1N NaOH (once) and 50 ml of brine (once). After drying over MgSO₄ and evaporation of solvent the residue is purified by FC in hexane/ether 1/1 to give 3.76 g of **2b** as an oil. ¹H-NMR (CDCl₃): δ = 7.35 - 7.15 m (10H); 4.65 m (1H); 4.5 s (2H); 4.15 d (2H); 3.5 t (2H); 3.25 dd (1H); 3.25 dd (1H); 2.95 m (2H); 2.7 dd (1H); 1.90 - 1.45 m (4H).

c*) 4S-(Benzyl)-3-(5-benzyloxy-2S-methyl-1-oxopentyl)-2-oxazolidinone 3b (Z = benzyl in Scheme 1)

[0061] All non-aqueous steps are carried out under argon. A solution of 205 g of compound **2b** in 800 ml of THF is added dropwise at -75° to 690 ml of a 1M solution of NaHMDS in THF. After completion of the addition (ca. 2h), the solution is stirred for an additional 30 min at -70° after which time a solution of 198 ml of methyl iodide in 800 ml of THF is added dropwise at the same temperature (ca. 45 min). The mixture is then stirred at -70° for 75 min, the cooling bath is removed and the mixture is allowed to warm to room temperature. After addition of 300 ml of THF/water 1/1 followed by 250 ml of saturated aqueous NH₄Cl the organic layer is separated and the remaining aqueous solution is extracted three times with 300 ml of t-butyl-methyl ether each. The combined organic extracts are evaporated to dryness and the residue is purified by FC in t-butyl-methyl ether/hexane 1/1 to yield a ca. 11/1 mixture of diastereoisomers. Recrystallization of this material from ethyl acetate/hexane (ca. 1/10) gave 98.5 g of **3a**, which was diastereomerically pure. M. p. 51.5 - 53.3 °C. ¹H-NMR (CDCl₃): δ = 7.5 - 7.15 m (10H); 4.65 m (1H); 4.45 s (2H); 4.1 m (2H); 3.75 m (1H); 3.45 m (2H); 3.25 dd (1H); 2.75 dd (1H); 1.90 - 1.45 m (4H); 1.20 d (3H).

d*) (S)-5-Benzyloxy-2-methyl-pentan-1-ol 4:

[0062] 150 ml of a 1M solution of LiAlH₄ in THF at 5° are added over a period of 20 min to a solution of 67.5 g of compound **3b** in 700 ml of dry THF are added. The reaction mixture is stirred at room temperature for 1 h and then quenched by addition of 17 ml of THF/water 10/7 followed by 6.5 ml of 4N NaOH and 15 ml of water. The resulting precipitate is removed by filtration, the residue washed with 250 ml of THF and the filtrate is evaporated. The residue is then redissolved in 250 ml of ethyl acetate and this solution extracted with 200 ml each of water, 1N NaOH, water, 1N HCl, and water followed by 300 ml of brine. The solvent is evaporated and the residue is three times co-evaporated with 100 ml of toluene. Vacuum distillation of the residue at 0.69 Torr gave 26 g of **4a** as a colourless oil (b. p. 105°). MS (C₁₃H₂₀O₂; 208.3): 209 [M+H]. ¹H-NMR (CDCl₃): δ = 7.35 - 7.25 m (5H); 4.5 s (2H); 3.45 m (4H); 1.8 - 1.4 m (3H); 1.2 m (1H); 0.95 d (3H).]

[0063] Further process after any of the 2 variants for synthesis of compound **4**:

e) (S)-1-Benzyloxy-5-(tert-butyl dimethylsilyloxy)-4-methylpentane 5

[0064] Imidazole (1.230 g, 18.06 mmol, 2.6 equiv) and *tert*-butyl-dimethylsilyl chloride (1.230 g, 9.03 mmol, 1.3 equiv)

are added to a solution of (S)-5-benzyloxy-2-methyl-pentan-1-ol 4 (1.447 g, 6.95 mmol) in dimethyl formamide (5.5 ml). The mixture is stirred for 1 h at 40 °C. Purification of the reaction mixture by flash column chromatography (pentane / diethyl ether 20:1) affords (S)-1-benzyloxy-5-(*tert*-butyldimethylsilyloxy)-4-methyl-pentane 5 (1.985 g, 89%) as a colourless oil (the reaction mixture is poured directly without aqueous workup onto a flash chromatography column which is pre-wetted with the eluent).

¹³C-NMR (100 MHz, CDCl₃): δ = 138.7; 128.3; 127.5; 127.4; 72.8; 70.8; 68.2; 35.6; 29.6; 27.2; 25.9; 18.3; 16.6; -5.4.

f) (S)-5-(*tert*-Butyldimethylsilyloxy)-4-methyl-pentan-1-ol 6

[0065] Three variants (i), (ii) or (iii) are possible:

(i) Catalytic Transfer Hydrogenolysis Protocol: 48.5 mg of Pd(OH)₂ on activated charcoal (20%) (Pearlman's catalyst) is added to a solution of (S)-1-benzyloxy-5-(*tert*-butyldimethylsilyloxy)-4-methyl-pentane 5 (485 mg, 1.5 mmol) in 12.0 ml of absolute ethanol and 6.0 ml of cyclohexene. The mixture is heated under reflux until the reaction is completed (tic monitoring). If starting material can still be detected after 8 h, some catalyst is added and refluxing is continued until the reaction is completed. After cooling to room temperature the catalyst is filtered off. The filtrate is concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 5:1) affords (S)-5-(*tert*-butyldimethylsilyloxy)-4-methyl-pentan-1-ol 6 (565 mg, 97%) as a colourless oil.

(ii) Debenzylation with Lithium 4,4'-di-*tert*-butyl-biphenyl (LiDTBBP):

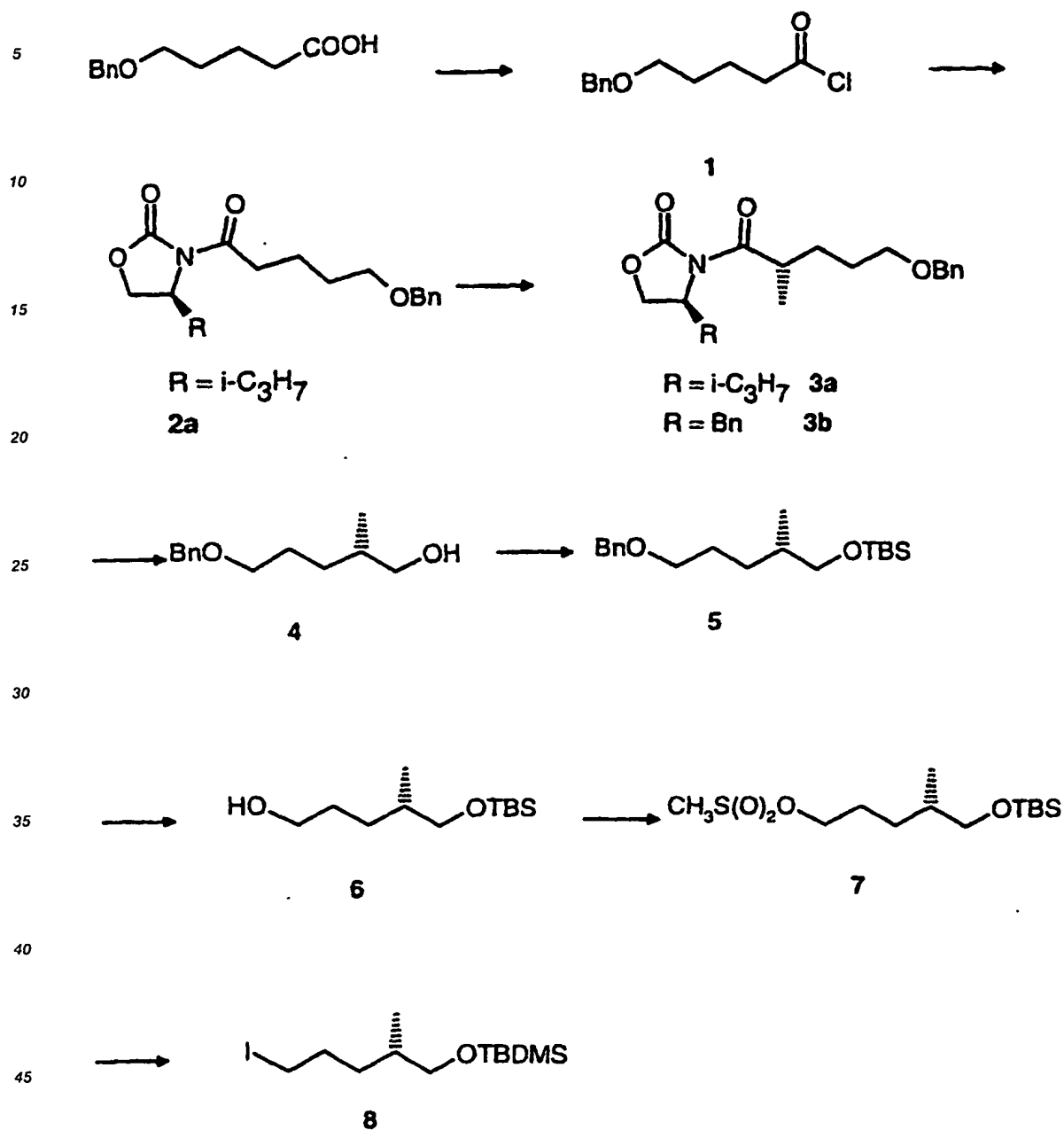
Preparation of LiDTBBP solution: With stirring, 4,4'-di-*tert*-butyl biphenyl (3.6 g) under an Argon atmosphere is added at 0 °C to a suspension of lithium (30% in mineral oil) in THF (30 ml). Stirring is continued for 2 h at r.t. The resulting deep green solution is added dropwise to a solution of (S)-1-benzyloxy-5-(*tert*-butyldimethylsilyloxy)-4-methyl-pentane 5 (673 mg, 2.09 mmol) in 10 ml of THF at -78 °C, until the colour of the mixture remains green (or until tic analysis shows completion of the reaction, respectively). Saturated aqueous NH₄Cl solution (10 ml) is added with stirring. The organic phase is separated and the aqueous layer is extracted with diethyl ether (3 x 50 ml). The combined organic extracts are dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 5:1) affords (S)-5-(*tert*-butyldimethylsilyloxy)-4-methyl-pentan-1-ol 6 (471 mg, 97%) as a colourless oil. ¹³C-NMR (100 MHz, CDCl₃): δ = 68.29; 63.36; 35.57; 30.24; 29.25; 25.98; 18.38; 16.77; -5.34

(iii) Catalytic hydrogenation: 102 g of compound 5 in 1800 ml of ethanol/cyclohexane 2/1 are hydrogenated over 10% Pd-C (10g) at room temperature and atmospheric pressure for 16h. After removal of the catalyst by filtration the solvents are evaporated and the residue is purified by silica gel chromatography in hexane/ethyl acetate 6/1 → 1/1 to yield 72 g of 6.

g) (S)-1-Methanesulfonyloxy-5-(*tert*-butyldimethylsilyloxy)-4-methyl-pentane 7

[0066] Triethyl amine (413 μl, 3.09 mmol, 1.53 equiv) and methanesulfonyl chloride (212 μl, 2.73 mmol, 1.35 equiv) is added to a solution of (S)-5-(*tert*-butyldimethylsilyloxy)-4-methyl-pentan-1-ol 6 (471 mg, 2.03 mmol) in 6.5 ml of dichloromethane. The mixture is stirred for 15 min at 0 °C, diluted with diethyl ether (30 ml), washed with water (5 ml), 1.0 M hydrochloric acid (5 ml), saturated aqueous sodium bicarbonate solution (5 ml), and brine (5 ml). The organic phase is separated, dried over magnesium sulfate and concentrated *in vacuo*. (S)-1-methanesulfonyloxy-5-(*tert*-butyldimethylsilyloxy)-4-methyl-pentane 7 (472 mg, 99%) is obtained as a colourless oil. ¹³C-NMR (100 MHz, CDCl₃): δ = 70.44; 67.98; 37.41; 35.31; 28.99; 26.80; 25.95; 18.34; 16.56; -5.37, -5.38 (-SiMe₂tBu).

Scheme 1

h) (S)-1-Iodo-5-(*tert*-butyldimethylsiloxy)-4-methyl-pentane **8**

[0067] Anhydrous sodium iodide (600 mg, 4.0 mmol, 2 equiv) is added to a solution of (S)-1-methanesulfonyloxy-5-(*tert*-butyldimethylsiloxy)-4-methyl-pentane **7** (622 mg, 2.0 mmol) in 3.0 ml of absolute acetone. The mixture is stirred for 2 h at 50 °C. 10 ml of a mixture of brine and water (1:1) are added, and the mixture is extracted with diethyl ether (3 x 20 ml). The combined organic extracts are dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 20:1) affords (S)-1-iodo-5-(*tert*-butyldimethylsiloxy)-4-methyl-pentane **8** (647 mg, 94%) as a colourless oil. FG 342.34; ^{13}C -NMR (100 MHz, CDCl_3): $\delta = 68.1, 35.1, 34.3, 31.3, 26.0, 16.7, 7.4, -5.3$

2) The Thiazole Segment (Scheme 2)

a) 4-Chloromethyl-2-methylthiazole **9**

[0068] A solution of thioacetamide (3.757 g, 50 mmol) is added dropwise to a saturated solution of 1,3-dichloroacetone (6.683 g, 50 mmol) in acetone. After a few minutes, a crystalline solid precipitates (the reaction can be initiated or accelerated by immersion of the reaction flask into an ultrasonic bath for a few seconds). In order to complete crystallisation, the reaction flask is left stand over night at r.t. The resulting suspension is filtered through a suction filter. The solid is washed with a few ml of acetone. A solution of the solid in ethanol (40 ml) is refluxed for 3 h. After the mixture is cooled to r.t. the solvent is removed *in vacuo*. Saturated aqueous sodium bicarbonate solution (50 ml) is added, and the mixture is extracted with diethyl ether (3 x 50 ml). The combined organic extracts are dried over magnesium sulfate and concentrated *in vacuo*. 4-Chloromethyl-2-methylthiazole **9** (7.138 g, 97%) is obtained as a pale yellow oil after complete evaporation of the solvent. ¹H-NMR (400 MHz, CDCl₃): δ(ppm) = 7.14 (s, 1H, H-5); 4.65 (s, 2H, -CH₂Cl); 2.72 (s, 3H, -CH₃); ¹³C-NMR (100 MHz, CDCl₃): δ(ppm) = 166.9; 151.6; 116.9; 40.7; 19.1

[0069] CAUTION: The reaction is strongly exothermic and it may not immediately take place after addition of the thioacetamide is started. The onset of the reaction can be delayed to the point where all of the thioacetamide has already been added, resulting in a vigorous and uncontrolled blow-up of the reaction mixture. It is therefore advisable to add the thioacetamide at 50°. If the reaction is not initiated after addition of 10% of the projected amount of thioacetamide the addition should be halted and only continued after onset of the reaction.

b) Diethyl-(2-methylthiazol-4-yl)-methanephosphonate **10**

[0070] A mixture of 4-chloromethyl-2-methylthiazole **9** (3.691 g, 25 mmol) and triethyl phosphite (6.64 ml, 50 mmol) is stirred for 6 h at 160 °C. Excess triethyl phosphite is distilled off under oil pump vacuum (4 mm). Purification of the residue by flash column chromatography (methanol / diethyl ether 19:1) yields diethyl-(2-methylthiazol-4-yl)-methanephosphonate **10** (5.066 g, 82%) as a colourless oil. Alternatively, the product can be isolated by high vacuum distillation (b. p. 110°C / 0.25 mm) together with some starting material **9** (b. p. 70 °C / 2mm). ¹³C-NMR (CDCl₃) δ = 164.3; 153.1; 142.2; 131.4; 125.7; 118.8; 114.9; 78.7; 68.3; 35.7; 34.6; 32.9; 27.8; 27.1; 25.9; 19.2; 18.3; 18.2; 16.7; 13.9; -4.7; -4.9; -5.4.

c) (3S)-Dihydro-3-hydroxy-2(3H)furanone [(S)-2-Hydroxy-γ-butyrolactone] **11**

[0071] Dropwise via syringe, a solution of (5S)-(2,2-cyclohexylidene-4-oxo-1,3-dioxolan-5-yl)acetic acid [synthesized starting from L-(-) malic acid, see S. Hanessian et al., J. Org. Chem. **58**, 7768 - 7781 (1993)] (15.04 g, 70.2 mmol) in 70 ml of dry THF is added to a mixture of 2.0 M BH₃-DMS complex (100 ml, 200.0 mmol) and B(OCH₃)₃ (24.2 ml, 200.0 mmol) in 175 ml of dry THF cooled at 0°C. The reaction mixture is stirred over night at room temperature and cooled to 0°C, and 70 ml of MeOH is added dropwise via syringe. The mixture is stirred for 1 h, and the solvent is removed under reduced pressure to afford a thick oil. This process is repeated twice with MeOH (105 ml) to afford a colourless oil. The crude product (a mixture of **11** and (5S)-(2-Hydroxyethyl)-2,2-cyclohexylidene-1,3-dioxolan-4-one) is dissolved in 175 ml of dichloromethane. p-Toluenesulfonic acid is added (1.335 g, 7.02 mmol, 0.1 eq) and the mixture is stirred for 24 h at r.t. Triethyl amine (980 µl) is added and the mixture is concentrated *in vacuo*. Purification of the residue by flash column chromatography (diethyl ether) affords (3S)-dihydro-3-hydroxy-2(3H)-furanone **11** (5.160 g, 72%) as a colourless oil. ¹³C-NMR (100 MHz, CDCl₃): δ(ppm) = 178.2; 67.4; 65.2; 30.8

d) (S)-2-(tert-Butyldimethylsilyloxy)-γ-butyrolactone **12**

[0072] Imidazole (241 mg, 3.54 mmol, 2.2 equiv) and tert-butyl-dimethylsilyl chloride (267 mg, 1.77 mmol, 1.1 equiv) are added to a solution of (3S)-dihydro-3-hydroxy-2(3H)-furanone **11** (164 mg, 1.61 mmol) in dimethyl formamide (1.5 ml). The mixture is stirred for 24 h at r.t. Purification of the reaction mixture by flash column chromatography (pentane / diethyl ether 10:1) affords (S)-2-(tert-butyldimethylsilyloxy)-γ-butyrolactone **12** (321mg, 93%) as a colourless oil. [α]_D²⁰ = -31.7; [α]₅₄₆²⁰ = -37.4 (c = 0.86, CHCl₃); ¹³C-NMR (100 MHz, CDCl₃): δ(ppm) = 175.8; 68.2; 64.7; 32.3; 25.6; 18.2; -4.8; -5.3

e) (3S)-3-(tert-Butyldimethylsilyloxy)-2-hydroxy-2-methyl-tetrahydrofuran **13**

[0073] Methyl lithium (670 µl [1.11 mmol, 1.1 equiv] of a 1.65 M solution in diethyl ether) is added dropwise to a stirred solution of (S)-2-(tert-butyldimethylsilyloxy)-γ-butyrolactone **12** (218 mg, 1.01 mmol) in THF (4.0 ml) cooled to -78 °C is added dropwise. After stirring at -78 °C for 3 h, the reaction is quenched by the addition of glacial acetic acid

(72 μ l, 1.26 mmol, 1.25 equiv). Diethyl ether (20 ml) and saturated aqueous sodium bicarbonate solution (10 ml) are added. After stirring for 5 min the organic layer is separated and the aqueous layer is extracted with diethyl ether (2 x 20 ml). The combined organic extracts are dried over magnesium sulfate and concentrated *in vacuo*. Crude (3*S*)-3-(*tert*-butyldimethylsilyloxy)-2-hydroxy-2-methyl-tetrahydrofuran **13** (235 mg, 93%) is obtained as a colourless crystalline solid (mixture of diastereomers) which is used for the synthesis of (S)-3,5-di-(*tert*-butyldimethylsilyloxy)-pentan-2-one **14** without further purification.

f) (S)-3,5-Di-(*tert*-butyldimethylsilyloxy)-pentan-2-one **14**

[0074] Imidazole (125 mg, 1.84 mmol, 2.2 equiv) and *tert*-butyl-dimethylsilyl chloride (139 mg, 0.92 mmol, 1.1 equiv) are added to a solution of (3*S*)-3-(*tert*-butyldimethylsilyloxy)-2-hydroxy-2-methyl-tetrahydrofuran **13** (194 mg, 0.83 mmol) in dimethyl formamide (800 μ l). The mixture is stirred for 24 h at r. t. Purification of the reaction mixture by flash column chromatography (pentane / diethyl ether 20:1) affords (S)-3,5-di-(*tert*-butyldimethylsilyloxy)-pentan-2-one **14** (226 mg, 78%) as a colourless oil. $[\alpha]_D^{20} = -11.8$; $[\alpha]_{546}^{20} = -14.1$ ($c = 1.0$, CHCl_3); $^1\text{H-NMR}$ (200 MHz, CDCl_3): δ (ppm) = 4.16 (dd, 1H); 3.8 - 3.5 (m, 2H); 2.16 (s, 3H); 1.9 - 1.7 (m, 2H); 0.92 (s, 9H); 0.88 (s, 2H); 0.06 (s, 6H); 0.04 (s, 3H), 0.03 (s, 3H)

g) (S,4E)-1,3-Di-(*tert*-butyldimethylsilyloxy)-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-ene **15**

[0075] (see D. Schinzer et al., Chem. Eur. J. **2**, 1477 - 1482 (1996)) *n*-Butyl lithium (23.5 ml [58.7 mmol, 1.2 equiv] of a 2.5 M solution in hexanes) is added dropwise to a stirred solution of diethyl-(2-methylthiazol-4-yl)-methanephosphonate **10** (14.64 g, 58.7 mmol, 1.2 equiv) in THF (150 ml) cooled to -78 °C. After stirring at -78 °C for 1 h, a solution of (S)-3,5-di-(*tert*-butyldimethylsilyloxy)-pentan-2-one **14** (16.96 g, 48.9 mmol, 1.0 equiv) in 100 ml of THF is added dropwise at -78 °C. The mixture is warmed to r.t. within 12 h. The reaction is quenched with saturated aqueous ammonium chloride solution (100 ml). The organic layer is separated and the aqueous layer is extracted with diethyl ether (3 x 100 ml). The combined organic extracts are dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography (gradient elution with pentane / dichloromethane 4:1 -> dichloromethane -> diethyl ether -> diethyl ether / methanol 10:1) affords (S,4E)-1,3-di-(*tert*-butyldimethylsilyloxy)-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-ene **15** (17.07 g, 38.6 mmol, 79%) as a colourless oil and some starting material (**10** and **14**). Alternatively, the crude product obtained after extraction can be directly used in the next step.

h) (S,4E)-3-(*tert*-butyldimethylsilyloxy)-1-hydroxy-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-ene **16 (see Schinzer et al., Chem. Eur. J. **2**, 1477-82 (1996))**

[0076] 20 ml of aqueous hydrofluoric acid (40 %) at 0 °C is added to a vigorously stirred solution of (S,4E)-1,3-di-(*tert*-butyldimethylsilyloxy)-4-methyl-5-(2-methylthiazol-4-yl)pent-4-ene **15** (13.255 g, 30.0 mmol) in 120 ml of diethyl ether and 120 ml of acetonitrile. Finely ground splinters of glass (133 mg) are added and the mixture is stirred for 2 h at 0 °C and analyzed by tlc. If starting material can still be detected another portion of hydrofluoric acid (20 ml) is added and stirring is continued for 1 h. The reaction is quenched by carefully adding solid sodium bicarbonate (84.0 g, 1.0 mol) within 15 min at 0 °C. After stirring for 30 min at 0 °C water is added until the salts dissolve (the pH is adjusted to 6 - 8 by further addition of sodium bicarbonate, if necessary). The mixture is extracted with dichloromethane (4 x 200 ml). The combined organic extracts are washed with brine (100 ml), dried over magnesium sulfate, and concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 4:1) affords (S,4E)-3-(*tert*-butyldimethylsilyloxy)-1-hydroxy-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-ene **16** (8.255 g, 84%) as a viscous, colourless oil.

i) (S,4E)-3-(*tert*-butyldimethylsilyloxy)-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-en-1-ol **17**

[0077] A solution of dimethyl sulfoxide (2.04 ml, 28.8 mmol, 2.4 equiv) in 6.0 ml of dichloromethane is added dropwise within 5 min to a stirred solution of oxalyl chloride (1.14 ml, 13.2 mmol, 1.1 equiv) in 30 ml of dichloromethane cooled to -78 °C. The mixture is stirred for 10 min at -70 °C. A solution of (S,4E)-3-(*tert*-butyldimethylsilyloxy)-1-hydroxy-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-ene **16** (3.93 g, 12.0 mmol) in 5 ml of dichloromethane is added dropwise within 5 min. The mixture is stirred for 30 min at -70 °C. The reaction is quenched by dropwise addition of triethyl amine (8.4 ml, 60.0 mmol). The mixture is warmed to r.t. within 45 min. Water (30 ml) is added and the mixture is stirred for 10 min. The organic layer is separated and the aqueous layer is extracted with dichloromethane (3 x 100 ml). The combined organic extracts are dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 5:2) affords (S,4E)-3-(*tert*-butyldimethylsilyloxy)-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-en-1-ol **17** (3.21 g, 82%) as a pale yellow oil.

j) (S,2Z,6E)-5-(*tert*-butyldimethylsilyloxy)-2-iodo-6-methyl-7-(2-methylthiazol-4-yl)-hepta-2,6-diene 18

[0078] Butyl lithium (5.14 ml [12.86 mmol, 1.96 equiv] of a 2.5 M solution in hexanes) is added dropwise to a stirred suspension of ethyl triphenylphosphonium iodide (13.12 mmol, 2.0 equiv) in 60 ml of THF cooled to 0°C. The resulting clear red ylide solution is added dropwise to a rapidly stirred solution of iodine (3.163 g, 12.46 mmol, 1.90 equiv) in 90 ml of THF cooled to -78 °C. The resulting yellow suspension is stirred vigorously for 10 min at -78 °C and for 30 min at -30 to -40 °C. 11.81 ml (11.81 mmol, 1.80 equiv) of a solution of sodium hexamethyldisilazide (NaHMDS, 1.0 M in THF) is added dropwise within 10 min at -30 °C. The mixture is stirred for 15 min at -30 °C. A solution of (S,4E)-3-(*tert*-butyldimethylsilyloxy)-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-en-1-al 17 (2.137g, 6.56 mmol) in 30 ml of THF is added dropwise within 10 min. The mixture is stirred for 10 min at -30 °C and quenched with saturated aqueous ammonium chloride solution (10 ml). Pentane (150 ml) is added and the mixture is filtered to a small plug of silica. The column is eluted with 400 ml of pentane / diethyl ether (4 : 1). The filtrate is concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 10:1) affords (S,2Z,6E)-5-(*tert*-butyldimethylsilyloxy)-2-iodo-6-methyl-7-(2-methylthiazol-4-yl)-hepta-2,6-diene 18 (1.640 g, 54%) as a pale yellow oil. ¹³C-NMR (100 MHz, CDCl₃): δ = 164.17; 152.85; 141.50; 131.89; 118.66; 115.01; 102.09; 76.45; 43.47; 33.42; 25.58; 18.98; 17.97; 13.87; -4.90, -5.23 (-SiMe₂tBu)

[0079] Alternatively, the iodoethyl phosphonium iodide that is formed as a precipitate in the first step of the above reaction sequence (upon addition of n-BuLi to ethyl phosphonium iodide) can be isolated by filtration and recrystallized from dichloromethane/THF. It is an air-stable crystalline yellow solid (m. p. ; ¹H-NMR (DMSO-d₆): δ = 8.1 - 7.7 m (15H); 6.3 m (1H); 2.55 dd (3H)).

The reaction scheme illustrates the synthesis of compound 18 from compound 9. The process begins with compound 9, which is a 2-methyl-4-(chloromethyl)thiazole. This is converted to compound 10, a diethyl phosphonate derivative of 9. Compound 10 then undergoes a series of reactions to form compound 15, which is a thiazole derivative with a TBDMSO group and an OTBDMS group. Compound 15 is then converted to compound 16, which has a hydroxyl group and an OTBDMS group. Compound 16 is further converted to compound 17, which has a carbonyl group and an OTBDMS group. Finally, compound 17 is converted to compound 18, which is a thiazole derivative with a TBDMSO group and an OTBDMS group.

[0080] 0.600 ml of a 1M solution of NaHMDS in THF are added at -78° to a suspension of 0.680 g of iodoethyl phosphonium iodide in 20 ml of THF. After stirring at -78° for 30 min, the yellow suspension is allowed to warm to -15°

over a period of 10 min, resulting in the formation of a red solution. After 20 min at -15° the solution is again cooled to -78° and 0.325 g of aldehyde 17 are added at this temperature. After 20 min at -78°, the reaction is quenched by adding 5 ml of saturated aqueous NH₄Cl at -78° and then worked up as described above.

3) Pd Coupling and Transformation of the Coupling Product (Scheme 5)

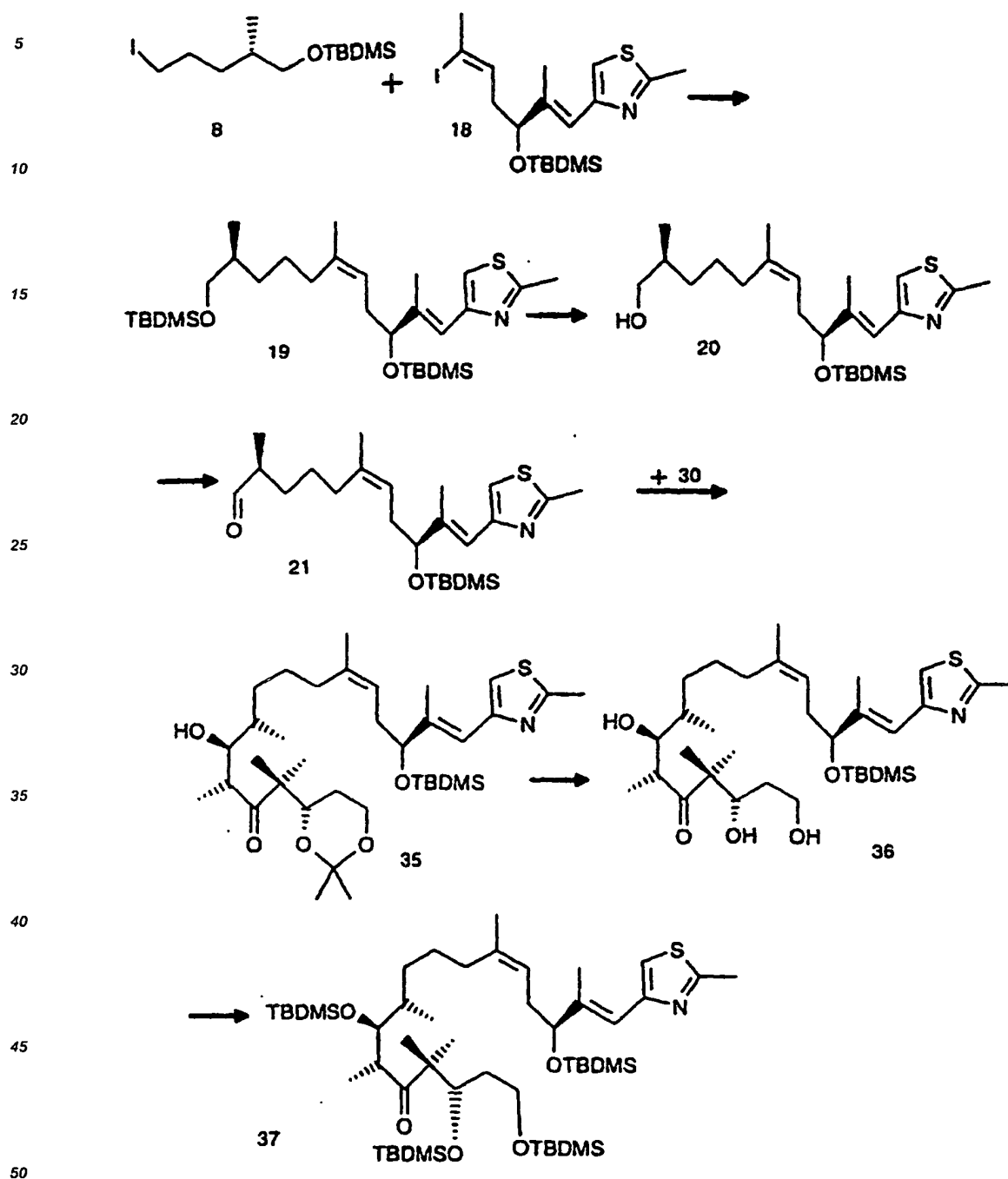
a) (6S, 10S, 2Z, 6E)-3,11-Di(*tert*-butyldimethylsilyloxy)-1-(2-methylthiazol-4-yl)-2,6,10-trimethyl-undeca-1,5-diene 19

[0081] 1,2-Dibromoethane (35 µl) is added to a suspension of powdered Zn/Cu couple [J. E. McMurry, J. G. Rico: Tetrahedron Lett. 30, 1169 - 1172 (1989)] (477 mg, 7.27 mmol, 2.3 equiv) in 11 ml of benzene under argon. The mixture is heated for a few seconds under reflux. After cooling to r.t., chlorotrimethylsilane (35 µl) is added and the mixture is stirred for 5 min. N,N-dimethylacetamide (750 µl) and (S)-1-iodo-5-(*tert*-butyldimethylsilyloxy)-4-methyl-pentane 8 (1.623 g, 4.74 mmol, 1.5 equiv) in 4.0 ml of benzene is added. The mixture is stirred for 2 h 30 min at 60 °C and analyzed by tlc. If starting material can still be detected, triethylsilyl trifluoromethanesulfonate (20 µl) or a few mg of mercury(II) acetate (for further activation of the metal) and 750 µl of N,N-dimethylacetamide is added, and the mixture is heated under reflux for 1 h. After cooling to r.t., Pd(PPh₃)₄ (140 mg, 4mol-%) is added and the mixture is stirred for 5 min. A solution of (S,2Z,6E)-5-(*tert*-butyldimethylsilyloxy)-2-iodo-6-methyl-7-(2-methylthiazol-4-yl)-hepta-2,6-diene 18 (1.463 g, 3.16 mmol) in 3.0 ml of benzene is added and the mixture is stirred for 30 min at 60 °C. After cooling to r.t., the reaction is quenched with saturated aqueous ammonium chloride solution (5 ml). The organic layer is separated and the aqueous layer is extracted with methyl *tert*-butyl ether (3 x 30 ml). The combined organic layers are dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 25:1) affords (6S,10S,2Z,6E)-3,11-di-(*tert*-butyldimethylsilyloxy)-1-(2-methylthiazol-4-yl)-2,6,10-trimethyl-undeca-1,5-diene 19 (1.458 g, 84%) as a colourless oil. Alternatively, benzene can be replaced by THF in the reaction. The yields decrease to 64%. => for spectroscopical data cf. ref. [K. C. Nicolaou et al., J. Am. Chem. Soc. 119, 7974 - 7991 (1997)].

b) (6S,10S,2Z,6E)-3(*tert*-butyldimethylsilyloxy)-1-(2-methylthiazol-4-yl)-2,6,10-trimethylundeca-1,5-dien-11-ol 20

[0082] The synthesis is carried out according to the Nicolaou procedure, see K. C. Nicolaou et al., J. Am. Chem. Soc. 119, 7974 - 7991 (1997) by reaction in methylene chloride:methanol (1:1, v/v) in the presence of campher sulfonic acid.

Scheme 5:



c) (6S,10S,2Z,6E)-3-(*tert*-Butyldimethylsilyloxy)-1-(2-methylthiazol-4-yl)-2,6,10-trimethylundeca-1,5-dien-11-al 21

[0083] A solution of (6S,10S,2Z,6E)-3-(*tert*-butyldimethylsilyloxy)-1-(2-methylthiazol-4-yl)-2,6,10-trimethylundeca-1,5-dien-11-ol 20 (306 mg, 0.7 mmol) in 5.0 ml of dichloromethane is added dropwise to a stirred solution of the Dess-Martin periodinane (386 mg, 0.91 mmol, 1.3 equiv) in 5.0 ml of dichloromethane and 73 μ l (0.91 mmol) of pyridine cooled to 0 °C. The mixture is stirred for 30 min at r.t. Diethyl ether (30 ml), pyridine (146 μ l, 1.82 mmol) and 0.5 M buffered (pH 7) aqueous sodium thiosulfate solution (10 ml) are added. The organic layer is separated off, and the

aqueous layer is extracted with methyl *tert*-butyl ether (2 x 20 ml). The combined organic layers are dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 5:1) affords (6S,10S,2Z,6E)-3-(*tert*-butyldimethylsilyloxy)-1-(2-methylthiazol-4-yl)-2,6,10-trimethylundeca-1,5-dien-11-ol **21** (295 mg, 97%) as a pale yellow oil; ¹³C-NMR: δ = 205.2; 164.4; 153.0; 142.0; 130.6; 126.4; 118.8; 115.0; 78.7; 46.2; 34.7; 30.0; 27.3; 26.9; 25.8; 19.2; 18.2; 13.9; 13.2; -4.7; -5.0.

4) The HYTRA Route to the Ethyl Ketone (Scheme 4)

(see P. Ellbracht et al., Chem. Ber. 122, 151 - 158 (1989))

a) Ethyl 2,2-dimethyl-3-ethyl-3-hydroxypentanoate **22**

[0084] A suspension of zinc dust (39.2 g, 0.6 mol) in 150 ml of THF and 150 ml of B(OCH₃)₃ is activated with 1,2 dibromoethane (3.0 ml) and chlorotrimethylsilane (3.0 ml). Diethyl ketone (95.7 ml, 0.9 mol) is added to the activated zinc suspension. Ethyl 2-bromo-2-methylpropanoate (Fluka, Buchs, Schweiz) is added dropwise within 90 min to the mixture. The mixture is stirred at r.t. for 20 h. The reaction is quenched by addition of concentrated aqueous ammonia solution (150 ml) at 0 °C. Glycerine (150 ml) and diethyl ether (150 ml) is added and the organic layer is separated. The aqueous layer is extracted twice with diethyl ether. The combined organic layers are dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by vacuum distillation affords ethyl 2,2-dimethyl-3-ethyl-3-hydroxypentanoate **22** (56.65 g, 47%) as a colourless liquid (b. p. 108 - 110 °C / 10 mbar). ¹³C-NMR (100 MHz, CDCl₃): δ = 179.2; 76.2; 60.9; 50.3; 28.2; 21.6; 14.1; 8.9

b) Ethyl (*E*)-2,2-Dimethyl-2-ethyl-3-pentenoate **23**

[0085] Ethyl 2,2-dimethyl-3-ethyl-3-hydroxypentanoate **22** (56.64 g, 280 mmol) is heated under reflux with phosphorous pentoxide (50.4 g, 355 mmol) in benzene (200 ml) for 15 min. Benzene is distilled off. The residue is extracted with diethyl ether (3 x 100 ml) and dissolved in saturated aqueous sodium bicarbonate solution (150 ml) at 0 °C. The resulting solution is neutralized by carefully adding sodium carbonate and extracted with diethyl ether (3 x 100 ml). The combined ethereal extracts are dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by vacuum distillation affords the title compound **23** (36.09 g, 70%) as a colourless liquid (b. p. 60 - 63 °C / 3 mbar). ¹³C-NMR (100 MHz, CDCl₃): δ = 177.2; 144.1; 118.5; 60.3; 48.4; 24.9; 21.7; 14.1; 13.9; 13.5

c) (*E*)-2,2-Dimethyl-3-ethyl-3-penten-1-ol **24**

[0086] Ethyl (*E*)-2,2-dimethyl-3-ethyl-3-pentenoate **23** (35.58 g, 193 mmol) is added dropwise to a suspension of lithium aluminium hydride (12.1 g, 320 mmol) in 81 ml of THF. The mixture is refluxed for 3 h, stirred for 16 h at r. t. and quenched with ice. The precipitate is filtered off by suction, washed several times with diethyl ether and hydrolyzed with 1 M hydrochloric acid. The aqueous solution is extracted with diethyl ether (3 x 100 ml). The combined ethereal extracts are dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by vacuum distillation affords the title compound **24** (15.87 g, 58%) as a colourless liquid (b. p. 105 - 106 °C / 30 mbar). ¹³C-NMR (100 MHz, CDCl₃): δ = 145.2; 120.5; 69.7; 42.0; 24.0; 20.0; 14.2; 13.6

d) (*E*)-2,2-Dimethyl-3-ethyl-3-pentenal **25**

[0087] A solution of dimethyl sulfoxide (18.7 ml, 260 mmol) in 80 ml of dichloromethane is added dropwise within 5 min to a stirred solution of oxalyl chloride (11 ml, 130 mmol) in 400 ml of dichloromethane cooled to -78 °C. The mixture is stirred for 10 min at -70 °C. A solution of (*E*)-2,2-Dimethyl-3-ethyl-3-penten-1-ol **24** (15.57 g, 110 mmol) in 60 ml of dichloromethane is added dropwise within 5 min. The mixture is stirred for 1 h at -70 °C. The reaction is quenched by dropwise addition of triethyl amine (76.3 ml, 550 mmol). The mixture is warmed to r.t. within 45 min. Water (400 ml) is added and the mixture is stirred for 10 min. The organic layer is separated off, and the aqueous layer is extracted with diethyl ether (3 x 200 ml). The combined organic extracts are dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by vacuum distillation affords the title compound **25** (9.7 g, 63%) as a colourless liquid (b. p. 85 - 86 °C / 28 mbar). ¹³C-NMR (100 MHz, CDCl₃): δ = 203.5; 141.4; 122.6; 52.7; 24.2; 20.9; 14.1; 13.8

e) (1S)-(1,2,2-Triphenyl-2-hydroxyethyl)-(3S,*E*)-4,4-dimethyl-5-ethyl-3-hydroxy-5-heptenoate **26**

[0088] 3.20 ml (8.0 mmol) of a 2.5 M solution of *n*-butyl lithium in hexanes at -78 °C is added to a solution of diisopropylamine (1.28 ml, 8.0 mmol) in 10 ml of THF cooled to -78 °C. The LDA solution is stirred for 30 min at 0 °C and

added dropwise to a solution of (S)-(-)-2-hydroxy-1,2,2-triphenyl acetate (1.330 g, 4.0 mmol) in 25 ml of THF at -78 °C. The mixture is stirred for 1 h at 0 °C. The resulting orange-red solution is cooled to -78 °C, and a solution of (E)-2,2-Dimethyl-3-ethyl-3-pentenal **25** (673 mg, 4.8 mmol, 1.2 equiv) in 5.0 ml of THF is added dropwise. The mixture is stirred for 90 min. The reaction is quenched with saturated aqueous ammonium chloride solution (30 ml). The organic layer is separated and the aqueous layer is extracted with dichloromethane (3 x 50 ml). The combined organic extracts are dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 3:1) affords the title compound **26** (1.41 g, 75%, 94% de) as a colourless crystalline solid (m. p. 100 °C). ¹³C-NMR (100 MHz, CDCl₃): δ = 172.2; 146.0; 144.7; 142.6; 135.6; 128.4; 128.3; 128.0; 127.8; 127.5; 127.3; 127.1; 126.3; 126.2; 120.3; 80.4; 78.9; 72.3; 44.0; 37.4; 21.9; 21.3; 20.2; 14.3; 13.6

(f) (E)-4,4-Dimethyl-5-ethyl-3S-hydroxyhept-5-enoic acid 27

[0089] Potassium hydroxide (163 mg, 2.5 mmol) is added to a solution of the ester (1.182 g, 2.5 mmol) in 29 ml of methanol and 8.3 ml of water. The mixture is heated under reflux for 2 h, cooled to r. t. and concentrated *in vacuo*. The resulting suspension is filtered by suction. The solid is washed with 50 ml of water. The combined aqueous layers are extracted with dichloromethane (2 x 50 ml) to remove traces of (S)-2,2,1-triphenyl ethanediol. The aqueous solution is cooled to 0 °C and acidified to pH 2.5 by dropwise addition of 6 N hydrochloric acid with vigorous stirring. The clear solution is saturated with solid sodium chloride and extracted with ethyl acetate (5 x 50 ml). The combined organic extracts are dried over magnesium sulfate and concentrated *in vacuo*. After complete evaporation, (E)-4,4-dimethyl-5-ethyl-3S-hydroxyhept-5-enoic acid **27** (442 mg, 88%) is obtained as a colourless crystalline solid. ¹³C-NMR (100 MHz, CDCl₃): δ = 178.5; 145.8; 121.0; 72.2; 44.0; 36.7; 22.5; 21.8; 20.4; 14.3; 13.7

g) (S)-(E)-4,4-Dimethyl-5-ethyl-5-heptene-1,3-diol 28

[0090] Lithium aluminium hydride (1.325 g, 35.0 mmol, 7.0 equiv) is added portionwise to a refluxing solution of (1S)-2,2,1-triphenyl-2-hydroxyethyl (3S,E)-4,4-dimethyl-5-ethyl-3-hydroxy-5-heptenoate **26** (2.364 g, 5.0 mmol) in diethyl ether (50 ml) within a period of 2 h. Refluxing is continued for 30 min. After cooling to 0 °C, the reaction is quenched dropwise with 1.35 ml water and 1.35 ml of aqueous NaOH (15%). Diethyl ether (40 ml) and water (2.0 ml) is added. The mixture is stirred for 1 h at r. t. until a white precipitate forms which is filtered off by suction through a small plug of celite. The precipitate is washed with diethyl ether (4 x 40 ml). The filtrate and the washings are combined and concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 2:1) affords (S)-2,2,1-Triphenyl-ethane-1,2-diol (922 mg, 99%) as a colourless, crystalline solid and (S)-(E)-4,4-Dimethyl-5-ethyl-5-heptene-1,3-diol **28** (836 mg, 90%) as a colourless oil. ¹³C-NMR (100 MHz, CDCl₃): δ = 146.2; 121.1; 75.8; 62.6; 44.4; 32.7; 22.8; 21.1; 20.1; 14.3; 13.6

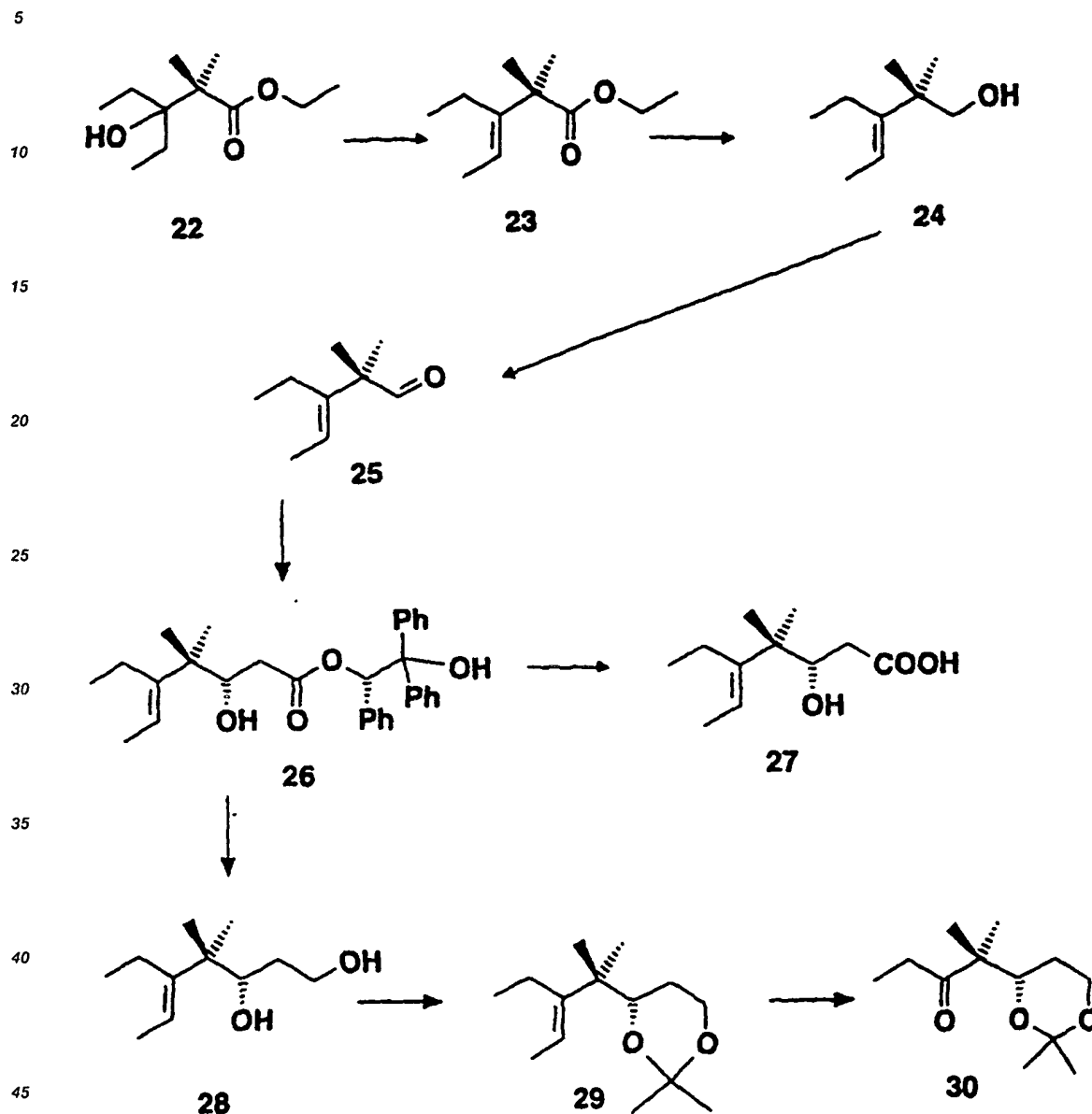
h) (S)-(E)-4-(2,2-Dimethyl-[1,3]dioxan-4-yl)-3-ethyl-2-methyl-pent-3-ene 29

[0091] Anhydrous copper sulfate (478 mg, 3.0 mmol, 1.5 equiv), p-toluenesulfonic acid monohydrate (76 mg, 0.4 mmol, 0.2 equiv), and pyridine (24 µl, 0.3 mmol, 0.15 equiv) are added to a solution of (S)-(E)-4,4-dimethyl-5-ethyl-heptane-1,3-diol **28** (372 mg, 2.0 mmol) in acetone (30 ml). The mixture is stirred for 24 h at r. t. Saturated aqueous sodium bicarbonate solution (40 ml) is added, and the aqueous layer is extracted with diethyl ether (4 x 60 ml). The combined organic extracts are dried over magnesium sulfate and carefully concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 40:1) affords the title compound **29** (812 mg, 90%) as a colourless oil. ¹³C-NMR (50 MHz, CDCl₃): δ = 146.2; 119.3; 98.3; 74.2; 60.4; 42.9; 29.9; 26.2; 24.3; 21.2; 19.2; 14.4; 13.7

i) (S)-2(2,2-Dimethyl-[1,3]dioxan-4-yl)-2-methyl-pentan-3-one 30 ("ethyl ketone")

[0092] Ozone in oxygen is bubbled through a stirred solution of (S)-(E)-4-(2,2-dimethyl-[1,3]dioxan-4-yl)-3-ethyl-4-methyl-pent-2-ene **29** (226 mg, 1.0 mmol) in dichloromethane (40 ml) at -78 °C until the blue colour of ozone persists. Triphenyl phosphine (262 mg, 1.2 equiv) is added. The reaction mixture is warmed to r.t. within 4 h and concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 5:1) affords (S)-2(2,2-dimethyl-[1,3]dioxan-4-yl)-2-methyl-pentan-3-one **30** (182 mg, 85%) as colourless crystals. ¹³C-NMR (CDCl₃) δ = 213.2; 98.4; 74.2; 59.8; 50.; 31.7; 30.0; 25.6; 21.0; 19.4; 19.0; 8.2.

Scheme 4



5. Alternative Synthesis of compound 30 (Scheme 3):

a) Compound 31:

[0093] Under an Ar atmosphere, 336 ml of triethyl borane are added slowly to 2.5 l of hexane at room temperature (ca. 25 min). To this solution, 187 ml of $\text{CF}_3\text{SO}_3\text{H}$ are added under cooling. After rinsing the dropping funnel with 180 ml of dichloromethane, the mixture is slowly warmed to 40° until gas evolution ceases (ca. 70 min). it is then cooled and a solution of 459 g of (2R)-N-acetylbomane-10,2-sultam (W. Oppolzer et al., *Tetrahedron Lett.* **1992**, 33, 2439) in 4 l of dichloromethane is added at 0° - 2° over a period of 20 min followed by a solution of 382 ml of diisopropylethyl amine (Hünig's base) in 1.5 l of dichloromethane (also at 0° - 2° ; ca 20 min). The reaction mixture is then cooled to -75° and a solution of 329 g of 2,2-dimethyl-3-oxo-pentanal (K. C. Nicolaou et al., *J. Am. Chem. Soc.* **1997**, 119,7974) in

300 ml of dichloromethane is added at the same temperature over a period of 35 min. After an additional 1.5 h at -70° - 75°, the reaction is quenched by addition of 400 ml of THF/water 3/1 followed by 3.5 l of saturated aqueous NH₄Cl. The solution is then concentrated and diluted with 2l of ethyl acetate plus 2l of water, and the organic layer is separated off. The remaining aqueous solution is extracted three times with 2 l of ethyl acetate, respectively, and the combined organic extracts are washed 6 times with 1 l of water and then once with 1 l of brine. Drying over Na₂SO₄ and evaporation of solvent gives a semi-crystalline yellow residue which is then recrystallized twice from ethylacetate/hexane to yield 316 g of **31** as a single diastereoisomer (white crystals). M. p.: 121 -122 °C. MS (C₁₉H₃₁NO₅S; 385.52): 386 [M+H]. ¹H-NMR (CDCl₃): δ = 4.3 m (1H); 3.85 m (1H); 3.45 dd (2H); 3.25 m (1H); 2.9-2.65 m (2H); 2.55 q (2H).

b) Compound 32:

[0094] To a solution of 409 g of compound **31** in 3 l of dichloromethane, 185 ml of 2,6-lutidine are added, followed by a solution of 292 ml of t-butyl-dimethylsilyl triflate in 200 ml of dichloromethane (both additions at approximately - 75°). The reaction mixture is stirred at -75° for 2.5h and then allowed to warm to room temperature over night. Then, the mixture is extracted three times with 1 l of water, respectively, the combined aqueous extracts are re-extracted twice with each time 1 l of dichloromethane, and the combined organic extracts are finally evaporated to dryness. The residue is recrystallized from ethanol/water to yield 485 g of **32** as white crystals. M. p.: 87 - 89 °C. MS (C₁₉H₄₅NO₅SSi; 499.78): 500 [M+H]. ¹H-NMR (CDCl₃): δ = 4.75 m (1H); 3.8 m (1H); 3.4 dd (2H); 2.95dd (1H); 2.75 dd (1H); 2.5 q (2H); 0.8 s (9H).

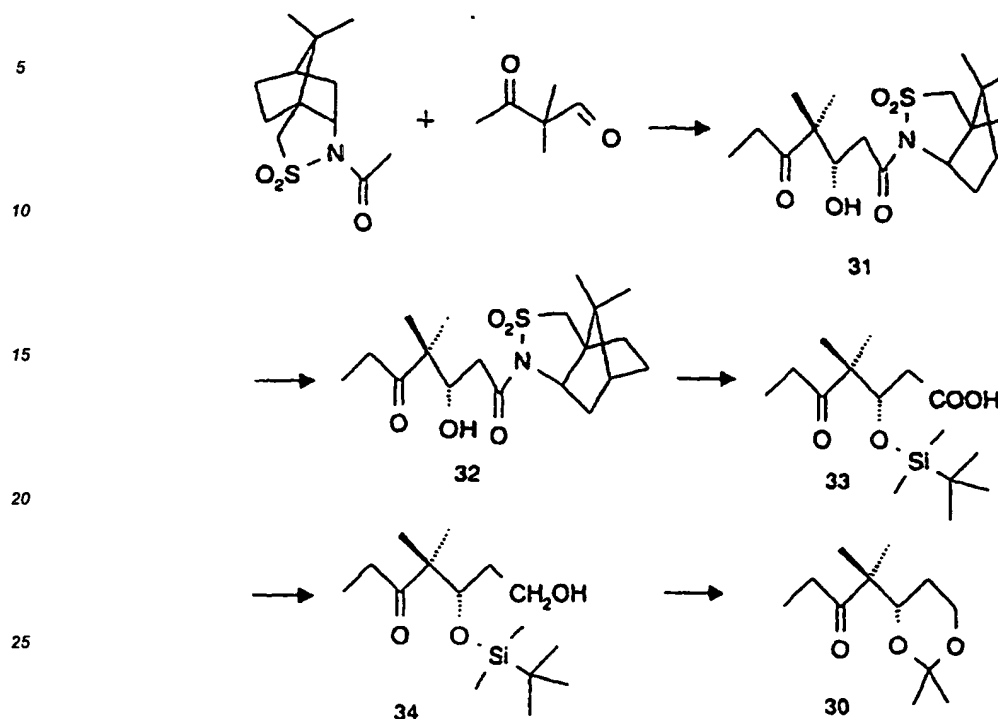
c) 3(S)-(tert-Butyl-dimethyl-silyloxy)-4,4-dimethyl-5-oxo-heptanoic acid 33:

[0095] To a solution of 10 g of compound **32** in 100 ml of THF/water 4/1, 0.772 g of LiOH are added, followed by 3.37 ml of 30% aqu. H₂O₂. After 7 h stirring at room temperature, 3.78 g of Na₂SO₃ are added to the mixture and the THF is removed by evaporation. 50 ml of ethyl acetate are added to the remaining aqueous suspension and the pH is adjusted to 6 by addition of 1 N HCl. The organic layer is then removed and the aqueous solution is extracted twice with ethyl acetate. The combined organic extracts are evaporated and the residue is suspended in 50 ml of hexane. After stirring at 0° C for 1 h the mixture is filtered, the filtrate evaporated and the residue purified by Flash Chromatography in dichloromethane/MeOH 97/3 -> 95/1 to yield 4.58 g of **33** as an oil. ¹H-NMR (CDCl₃): δ = 4.45 m (1H); 3.6 - 3.4 m (3H); 2.3 dd (1H); 1.15 s (3H); 1.05 s (3H); 1.00 t (3H); 0.85 s (9H).

d) 5(S)-(tert-Butyl-dimethyl-silyloxy)-7-hydroxy-4,4-dimethyl-heptan-3-one 34:

[0096] 1.017 ml of trimethyl borate, followed by 0.607 ml of BH₃ x Me₂S, are added to a solution of 0.689 g of compound **33** in 20 ml of THF at 0°. The reaction mixture is stirred at 0° for 2h and at 15° for 6h. It is then cooled to 0°, 3 ml of water are added dropwise and the mixture is stirred for 10 min. The solvents are subsequently evaporated and the residue is re-evaporated three times after addition of methanol and then purified by flash chromatography using dichloromethane/ ether 98/2 to give 0.71 g of **34** as an oil. MS (C₁₅H₃₂O₃Si; 288): 271 [M - OH]; 231 [M - t-butyl].

Scheme 3:



e) (S)-2(2,2-Dimethyl-[1,3]dioxan-4-yl)-2-methyl-pentan-3-one 30:

[0097] A solution of 0.200 g of compound **34** in 5 ml of acetone/ CF_3COOH is heated to 35° for 18h. Triethyl amine (1 ml) is then added to the mixture at 0° followed by 20 ml of diethyl ether. The solution is then three times extracted with 10 ml of water each, dried, and the solvent evaporated. FC of the residue in hexane/ether 3/1 (+ 1% of triethyl amine) gives 0.118 g of **30**. MS ($\text{C}_{12}\text{H}_{22}\text{O}_3$; 214): 215 [M+H]. $^1\text{H-NMR}$ (CDCl_3): δ = 4.05 - 3.80 m (3H); 2.5 q (2H); 1.40 s (3H); 1.30 m (includ. s) (4H); 1.10 s (3H); 1.00 s (3H); 0.95 t (3H).

6) The Aldol Reaction and the Final Steps to of the Formal Total Synthesis of Epothilone B (Scheme 5)

a) The Aldol Reaction to yield compound 35

[0098] A solution of (S)-2(2,2-Dimethyl-[1,3]dioxan-4-yl)-2-methyl-pentan-3-one **30** (64 mg, 0.3 mmol) in THF (500 μl) is added dropwise at -78°C to a freshly prepared solution of LDA [$n\text{-BuLi}$ (118 μl , 2.5 m solution in hexanes, 0.294 mmol, 0.98 equiv) is added to a solution of diisopropylamine (41.6 μl , 0.294 mmol) in THF (500 μl) at 0°C . The mixture is stirred for 30 min at 0°C . Then, the solution is stirred for 1 h at -78°C . A solution of (6S,10S,2Z,6E)-3-(*tert*-butyldimethyl-silyloxy)-1-(2-methylthiazol-4-yl)-2,6,10-trimethyl-undeca-1,5-dien-11-al **21** (65 mg, 0.15 mmol, 0.5 equiv) in THF (600 μl) is added dropwise, and stirring is continued for 20 min at -78°C . The mixture is quenched by dropwise addition of saturated aqueous ammonium chloride solution (2 ml). The organic layer is separated and the aqueous layer is extracted with diethyl ether (3 x 5 ml). The combined organic extracts are dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 10:1, then 5:1) affords 83 mg (85 %) of **35** as colourless oil. Major diastereoisomer: $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ = 222.81; 164.27; 153.28; 142.49; 136.94; 121.44; 118.65; 114.89; 98.45; 79.08; 74.74; 74.38; 59.89; 51.60; 41.28; 35.42; 35.32; 33.04; 32.40; 29.76; 25.85; 25.24; 25.15; 23.51; 21.55; 19.19; 19.03; 18.58; 18.24; 15.35; 13.92; 9.31; -4.65; -4.93

b) Triol compound 36

[0099] PPTS (6.0 mg, 24 μmol , 0.6 equiv) is added to a solution of the ANTICRAM aldol product **35** (26 mg, 0.04

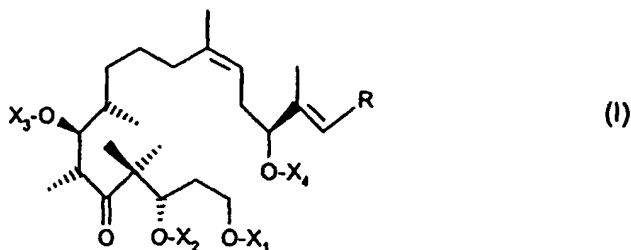
mmol) in methanol (500 μ l). The mixture is stirred for 22 h. Another portion of PPTS (4.0 mg, 16 μ mol, 0.4 equiv) is added and stirring is continued for 50 h. The solvent is removed *in vacuo* and the residue is purified by flash column chromatography with diethyl ether. The triol **36** (21 mg, 86 %) is obtained as a colourless oil. ^{13}C -NMR (CDCl_3) δ = 223.3; 154.5; 153.1; 142.7; 136.8; 121.6; 118.7; 114.8; 79.2; 76.3; 74.4; 62.1; 52.7; 41.1; 35.6; 35.4; 32.8; 32.5; 32.3; 25.8; 25.1; 23.5; 21.6; 19.1; 18.5; 18.2; 15.5; 13.8; 10.1; -4.0; -4.3.

c) Tetrakis Silyl Ether **37** (compound of formula I wherein each of X_1 to X_4 is tert-butyl dimethylsilyl and R is 2-methylthiazol-4-yl)

[0100] 2,6-lutidine (29 μ l, 247.5 μ mol, 2.5 equiv) is added to a solution of the triol **32** (20.0 mg, 33 μ mol) in dichloromethane (200 μ l). The mixture is cooled to -50 $^\circ\text{C}$ and tert-butyl-dimethylsilyltrifluoromethanesulfonate (34 μ l, 148.5 μ mol, 1.5 equiv) is added. The mixture is warmed 0 $^\circ\text{C}$ and stirring is continued for 2 h at 0 $^\circ\text{C}$. The solvent is removed *in vacuo* and the residue is purified by flash column chromatography (pentane / diethyl ether 20:1). The tetrakis silyl ether **33** (30 mg, 95%) is obtained as a colourless oil. ^{13}C -NMR (100 MHz, CDCl_3): δ = 218.25; 164.27; 153.29; 142.49; 136.75; 121.56; 118.68; 114.90; 78.99; 77.45; 74.04; 60.99; 53.66; 45.05; 38.95; 38.11; 35.34; 32.57; 31.04; 29.70; 26.24; 26.12; 25.97; 25.85; 24.50; 23.53; 19.40; 19.22; 18.52; 18.30; 18.24; 18.13; 17.56; 15.20; 13.93; -3.65; -3.67; -3.75; -3.98; -4.64; -4.92; -5.22; -5.25

Claims

1. A method for the preparation of a compound of the formula I,



wherein R is a heterocyclyl moiety and X_1 , X_2 , X_3 and X_4 are, independently of each other, protecting groups, characterized in that a compound of the formula II



wherein Y is the radical of an organic or inorganic acid devoid of its dissociable hydrogen, and X is a protecting group as described above for X_1 to X_4 , especially benzyl; is reacted with an oxazolidone of the formula III



wherein Z' is lower alkyl or phenyl-lower alkyl in an appropriate solvent either (i) in the presence of a strong base, especially methyl magnesium bromide, and then of an appropriate tertiary amino base, such as 4-dimethylaminopyridine; or (ii) in the presence of an alkali metal alkylid; at low temperatures, yielding a compound of the formula IV,



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40



55



pound of the formula I;
in parallel to that sequence of reactions,

a) a compound of the formula XI,



wherein R is as described under formula I and Hal is halogen is reacted with a tri-alkyl phosphite to yield a phosphonate compound of the formula XII,



wherein R is as defined under formula I and each of A is alkyl;

independently, (5S)-(2,2-cyclohexylidene-)-4-oxo-1,3-dioxolane is reacted with $\text{BH}_3\text{-Me}_2\text{S}$ complex and $\text{B}(\text{OCH}_3)_3$ and methanol to yield 3(S)-dihydro-3-hydroxy-2(3H)-furanone (compound 11 in reaction scheme 2); that is then protected by introduction of a protecting group X_4 to yield a compound of the formula XIII,



wherein X_4 is a protecting group; the compound of formula XIII is then reacted with an methyl metal or methyl metal derivative to the compound of the formula XIV,



wherein X_4 is as defined under formula XIII; the compound of formula XIV is reacted with a further reagent capable of introducing a protecting group yielding a compound of the formula XV,



wherein X and X_4 are a protecting group, which compound is then reacted with a phosphonate compound of the formula XII given above in the presence of an strong base yielding a compound of the formula XVII,



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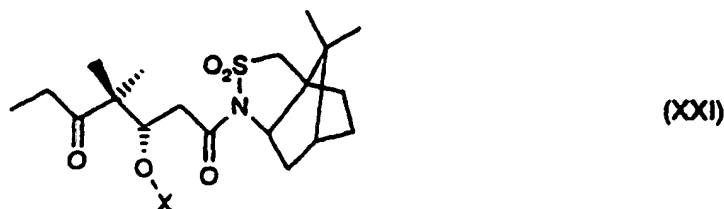
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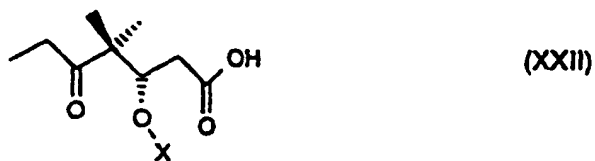
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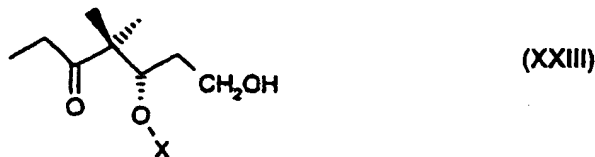
(b) **30** can be obtained by reaction of (2R)-N-acetylbornane-10,2-sultam in the presence of a dialkylborane triflate or dialkylborane chloride and after addition of a tertiary nitrogen base, with 2,2-dimethyl-3-oxo-pentanal that leads to the sultam product **31**, which is then reacted, in the presence of a tertiary nitrogen base, with a reagent appropriate for the introduction of a protecting group to give a compound of the formula **XXI**



wherein X is a protecting group; the compound of formula **XXI** is then converted into the corresponding free acid of the formula **XXII** by reaction with an appropriate aqueous base

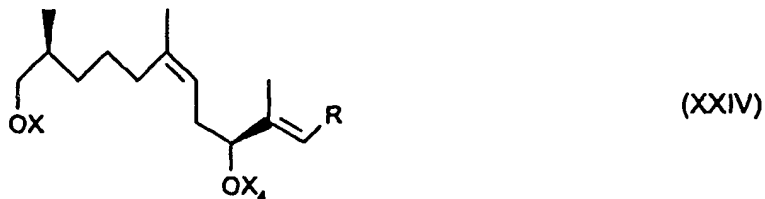


wherein X is as defined under formula **XXI**; the compound of formula **XXII** is then reduced to the corresponding alcohol of the formula **XXIII**

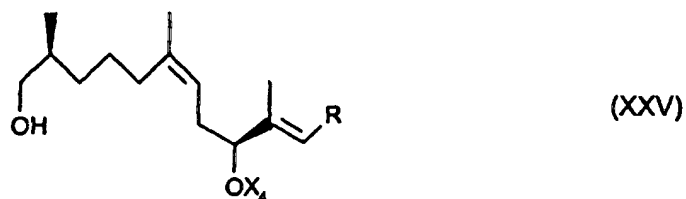


wherein X is as defined under formula **XXI**, and finally that compound is deprotected and transformed into compound **30** by reaction in acetone/acid, such as acetone/trifluoroacetic acid;

the compound **30** being the third intermediate for the convergent synthesis of the compound of the formula I; and, in a next step, first the two intermediates of the formulae X and XX are coupled by reaction of the compound of the formula X with a suspension of powdered Zn/Cu couple in the presence of an activator, in the presence of halotrialkylsilane, and then addition of Palladium-tetrakis(triphenylphosphin) in an appropriate solvent, and addition of the compound of formula XX, yielding a compound of the formula **XXIV**,



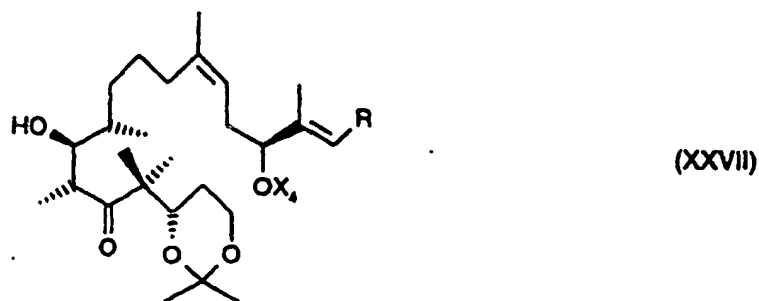
wherein X and X₄ each are a protecting group and R is as defined under formula I; the compound of the formula **XXIV** is then selectively deprotected to give a compound of the formula **XXV**,



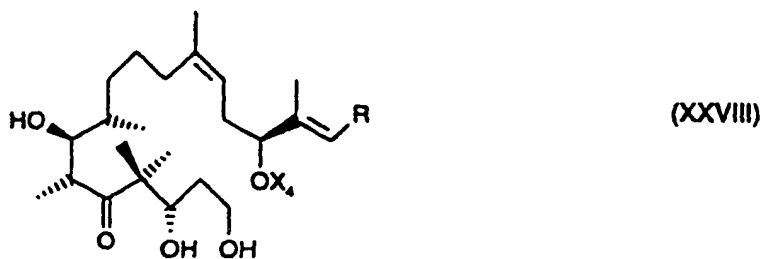
10 wherein X_4 and R are as defined under formula XXIV; the compound of the formula XXV is then oxidized with an appropriate oxidant to the corresponding aldehyde of the formula XXVI



25 wherein X_4 and R are as defined under formula XXIV; then, the third intermediate of the convergent synthesis, compound 30, is reacted with the compound of the formula XXVI in an Aldol reaction, resulting in a compound of the formula XXVII,

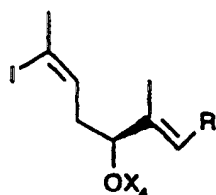


40 wherein X_4 and R are as defined under formula I; the compound of the formula XXVII is then deprotected under removal of the acetal moiety, yielding a compound of the formula XXVIII,



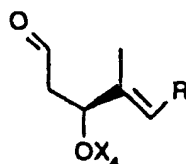
55 wherein X_4 and R are as defined under formula I; and finally, the compound of the formula I is obtained by introduction of protecting groups X_1 , X_2 and X_3 with appropriate reagents.

2. A method of synthesis of a compound of the formula XX,



(XX)

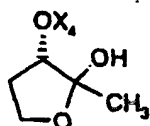
wherein R is a heterocyclic moiety and X_4 is a protecting group, characterized in that a compound of the formula XIX



(XIX)

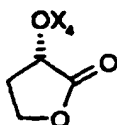
wherein R and X_4 are as defined under formula XX, is, by reaction with an strong base and iodine in the presence of triphenylphosphonium iodide and subsequent addition of the same or another strong base as above converted into a compound of the formula XX.

3. A method of synthesis of a compound of the formula XIV,



(XIV)

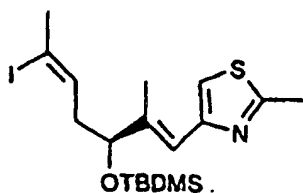
wherein X_4 is a protecting group, characterized in that a compound of the formula XIII,



(XIII)

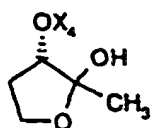
wherein X_4 is a protecting group, is reacted with an methyl metal or methyl metal derivative.

4. A compound of the formula

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wherein TBDMS is tert-butyldimethylsilyl.

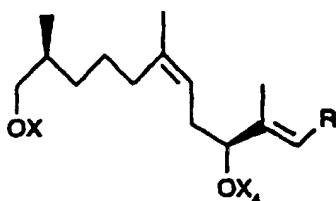
5. A compound of the formula XIV



(XIV)

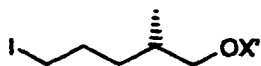
wherein X_4 is a protecting group other than tert-butyldimethylsilyl.

6. A method of synthesis for a compound of the formula XXIV,



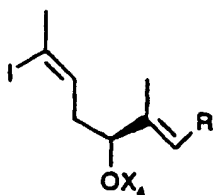
(XXIV)

wherein X and X_4 each are a protecting group, and R is a heterocyclyl moiety, characterized in that a compound of the formula X



(X)

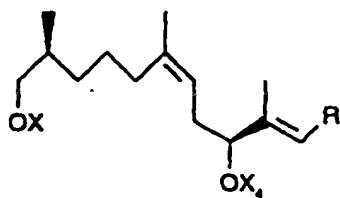
wherein X' is a protecting group, is coupled by reaction with a suspension of powdered Zn/Cu couple in the presence of an activator and of a halotrialkylsilane, and then addition of a Pd(0)-complex in an appropriate solvent, with a compound of the formula XX



(XX)

wherein X_4 is a protecting group and R is a heterocyclyl moiety.

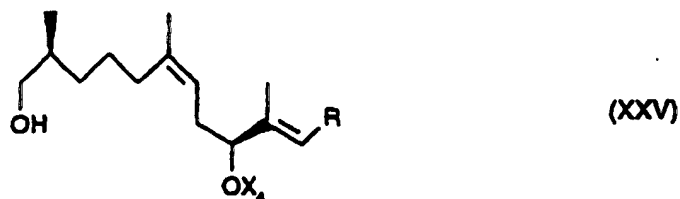
7. A compound of the formula



(XXIV)

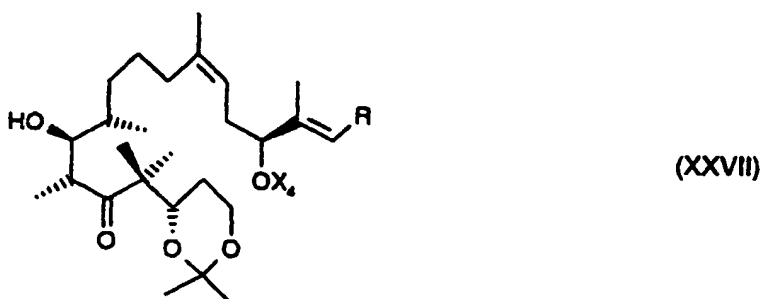
wherein X and X_4 each are a protecting group, and R is a heterocyclyl moiety, in the essentially pure cis-form.

8. A compound of the formula XXV,



wherein X₄ is a protecting group and R is a heterocyclyl moiety in the essentially pure cis-form.

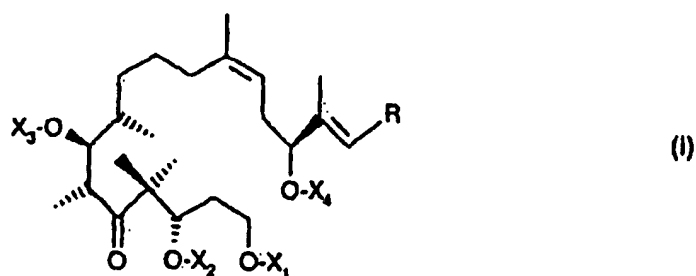
9. A compound of the formula XXVII,



wherein X₄ is a protecting group and R is a heterocyclyl moiety.

Patentansprüche

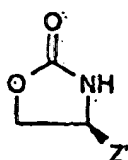
1. Verfahren zur Herstellung einer Verbindung der Formel I



worin R für einen Heterocyclylrest steht und X₁, X₂, X₃ und X₄ unabhängig voneinander für Schutzgruppen stehen, gekennzeichnet durch Umsetzung einer Verbindung der Formel II

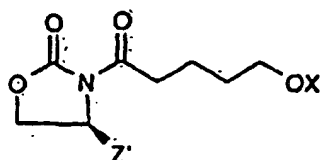


worin Y für den Rest einer organischen oder anorganischen Säure ohne deren dissoziierbarem Wasserstoff steht und X für eine Schutzgruppe gemäß obiger Beschreibung für X, bis X₄ steht, insbesondere Benzyl, mit einem Oxazolidon der Formel III



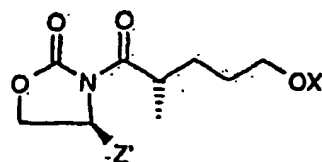
(III)

worin Z' für Niederalkyl oder Phenylniederalkyl steht, in einem geeigneten Lösemittel entweder (i) in Gegenwart einer starken Base, insbesondere Methylmagnesiumbromid, und dann einer geeigneten tertiären Aminobase, wie 4-Dimethylaminopyridin, oder (ii) in Gegenwart eines Alkalimetallalkylids bei niedrigen Temperaturen unter Bildung einer Verbindung der Formel IV



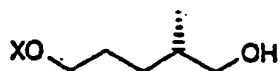
(IV)

worin X und Z' die oben angegebenen Bedeutungen haben, C-Methylierung der Verbindung der Formel (IV) wird unter Bildung einer Verbindung der Formel V



(V)

worin X und Z' wie oben definiert sind, reduktive Spaltung dieser Verbindung unter Freisetzung der Verbindung der Formel VI



(VI)

worin X wie oben definiert ist, Einführung einer Schutzgruppe X' in diese Verbindung, die aus den oben für X₁ bis X₄ erwähnten Schutzgruppen ausgewählt ist, sich aber von X in der Formel VI unterscheidet, an der freien Hydroxygruppe hiervon, welche eine Abspaltung der Schutzgruppe X in der Verbindung der Formel VI ohne Beeinträchtigung der neu eingeführten Schutzgruppe X' erlaubt, unter Bildung einer bisgeschützten Verbindung der Formel VII



(VII)

worin X und X' wie oben definiert sind, Abspaltung der Schutzgruppe X aus der Verbindung VII unter geeigneten Bedingungen zur Bildung einer Verbindung der Formel VIII



(VIII)

worin X' wie bei der Verbindung der Formel VII definiert ist, Umsetzung der Verbindung der Formel VIII mit einem

Halogenid einer organischen Sulfonsäure unter Bildung des entsprechenden Sulfonsäureesters der Formel IX



worin Q für ein organisches Sulfonyl steht, und Umsetzung dieses Sulfonylesters mit einem Metalliodid unter Bildung der entsprechenden Iodidverbindung der Formel X

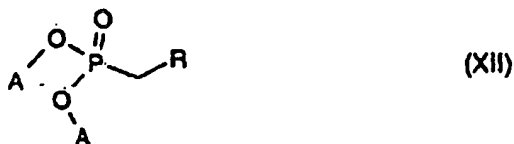


worin X' wie oben definiert ist, wobei diese Verbindung der Formel X das erste von drei Zwischenprodukten für die konvergente Synthese der Verbindung der Formel 1 darstellt, durch parallel zur obigen Folge von Reaktionen

a) Umsetzung einer Verbindung der Formel XI



worin R wie bei der Formel I definiert ist und Hal für Halogen steht, mit einem Trialkylphosphit unter Bildung einer Phosphonatverbindung der Formel XII

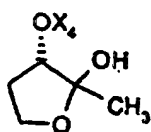


worin R wie bei der Formel I definiert ist und jedes A für Alkyl steht,

unabhängig davon Umsetzung von (5S)-(2,2-Cyclohexylden)-4-oxo-1,3-dioxolan mit dem Komplex $\text{BH}_3\text{-Me}_2\text{S}$ und $\text{B}(\text{OCH}_3)_3$ und Methanol unter Bildung von 3(S)-Dihydro-3-hydroxy-2(3H)-furanon (Verbindung 11 im Reaktionsschema 2), Schutz dieser Verbindung durch Einführung einer Schutzgruppe X_4 unter Bildung einer Verbindung der Formel XIII

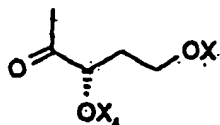


worin X_4 für eine Schutzgruppe steht, Umsetzung der Verbindung der Formel XIII mit einem Metallmetall oder Metallmetallderivat unter Bildung der Verbindung der Formel XIV



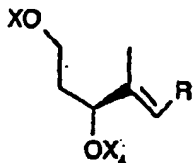
(XIV)

worin X_4 wie bei der Formel XIII definiert ist, Umsetzung der Verbindung der Formel XIV mit einem weiteren, zur Einführung einer Schutzgruppe befähigten Reagens unter Bildung einer Verbindung der Formel XV



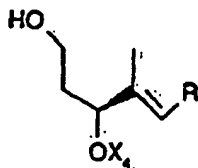
(XV)

worin X und X_4 für Schutzgruppen stehen, Umsetzung dieser Verbindung mit einer Phosphonatverbindung der Formel XII in Gegenwart einer starken Base unter Bildung einer Verbindung der Formel XVII



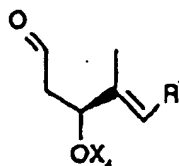
(XVII)

worin X und X_4 wie bei der Formel XIII definiert sind und R wie bei der Formel I definiert ist, partielle Abspaltung der Schutzgruppe X von der Verbindung der Formel XVII unter geeigneten Bedingungen unter Bildung einer Verbindung der Formel XVIII



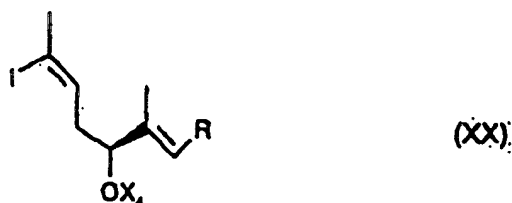
XVIII

worin die Reste X_4 und R wie bei der Formel XVII definiert sind, selektive Oxidation der Verbindung der Formel XVIII zum entsprechenden Aldehyd der Formel XIX



(XIX)

worin R und X_4 wie bei der Formel XVII definiert sind, Umsetzung dieser Verbindung mit einem Alkylalkalimetall und Iod in Gegenwart von Triphenylphosphoniumiodid (entweder unter Isolierung des Iodethylphosphoniumiodids oder in einer Eintopfsynthese) und anschließenden Zusatz einer unterschiedlichen Base oder der gleichen Base wie oben, insbesondere Natriumhexamethyldisilazid, unter Umwandlung zu einer Verbindung der Formel XX



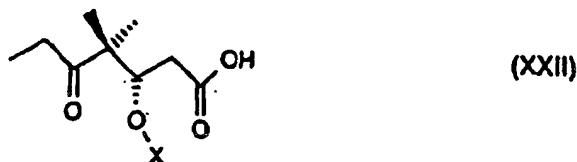
worin R und X₄ wie bei der Formel XVII definiert sind,
wobei diese Verbindung der Formel XX das zweite von drei Zwischenprodukten für die konvergente Synthese der Verbindung der Formel I darstellt,
Herstellung des dritten Zwischenprodukts für die konvergente Synthese nach einem der im folgenden beschriebenen zwei Wege (a) und (b) entweder unter

(a) Umsetzung von Diethylketon in Gegenwart von aktiviertem Zinkstaub und von B(OCH₃)₃ mit Ethyl-2-brom-2-methylpropanoat unter Bildung von Ethyl-2,2-dimethyl-3-ethyl-3-hydroxypentanoat **22**, Umsetzung dieser Verbindung mit einem Dehydratisierungsmittel zu Ethyl-(E)-2,2-dimethyl-2-ethyl-3-pentenoat **23**, Umsetzung dieser Verbindung in Gegenwart eines geeigneten Komplexhydrids zu (E)-2,2-Dimethyl-3-ethyl-3-penten-1-ol **24**, Oxidation dieser Verbindung mit einem geeigneten Oxidans zu (E)-2,2-Dimethyl-3-ethyl-3-pentenal **25**, Umsetzung dieser Verbindung mit (S)-(-)-2-Hydroxy-1,2,2-triphenylacetat in Gegenwart einer starken Base zu (1S)-2,2,1-Triphenyl-2-hydroxyethyl-(3S,E)-4,4-dimethyl-5-ethyl-3-hydroxy-5-heptenoat **26**, Transformation dieser Verbindung durch Umsetzung mit einem geeigneten Komplexhydrid zu (S)-(E)-4,4-Dimethyl-5-ethyl-5-hepten-1,3-diol **28**, Umwandlung dieser Verbindung durch Umsetzung mit Aceton in Gegenwart von wasserfreiem Kupfersulfat, einer starken organischen Base und einer tertiären Stickstoffbase unter Bildung von (S)-(E)-(2,2-Dimethyl-[1,3]dioxan-4-yl)-3-ethyl-2-methylpent-3-en **29**, und Umwandlung dieser Verbindung durch Ozonolyse zu Ethylketon-(S)-2-(2,2-dimethyl-[1,3]dioxan-4-yl)-2-methyl-pentan-3-on **30** wobei diese Verbindung 30 das dritte Zwischenprodukt für die konvergente Synthese darstellt oder optional unter

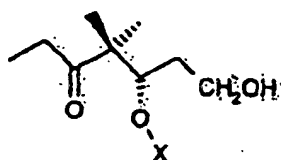
(b) Herstellung der Verbindung **30** durch Umsetzung von (2R)-N-Acetylbornan-10,2-sultam in Gegenwart eines Dialkylborantriflats oder Dialkylboranchlorids und nach Zusatz einer tertiären Stickstoffbase mit 2,2-Dimethyl-3-oxopentanal unter Bildung des Sultamprodukts **31**, Umsetzung dieser Verbindung in Gegenwart einer tertiären Stickstoffbase mit einem zur Einführung einer Schutzgruppe geeigneten Reagens unter Bildung einer Verbindung der Formel XXI



worin X für eine Schutzgruppe steht, Überführung der Verbindung der Formel XXI durch Umsetzung mit einer geeigneten wässrigen Base zur entsprechenden freien Säure der Formel XXII



worin X wie bei der Formel XXI definiert ist, Reduktion der Verbindung der Formel XXII zum entsprechenden Alkohol der Formel XXIII

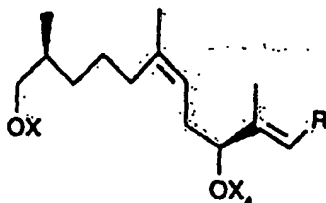


(XXIII)

worin X wie bei der Formel XXI definiert ist, und abschließende Abspaltung der Schutzgruppe von dieser Verbindung sowie Umwandlung der so erhaltenen Verbindung zur Verbindung **30** durch Umsetzung in Aceton/Säure, wie Aceton/Trifluoressigsäure,

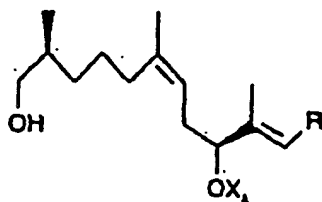
wobei diese Verbindung **30** das dritte Zwischenprodukt für die konvergente Synthese der Verbindung der Formel I darstellt,

und in einer nächsten Stufe Kupplung des ersten der beiden Zwischenprodukte der Formeln X und XX durch Umsetzung der Verbindung der Formel X mit einer Suspension eines pulverförmigen Zn/Cu-Paars in Gegenwart eines Aktivators und eines Halogentrialkylsilans und unter anschließendem Zusatz von Palladiumtetrakis (triphenylphosphin) in einem geeigneten Lösemittel und Zugabe der Verbindung der Formel XX unter Bildung einer Verbindung der Formel XXIV



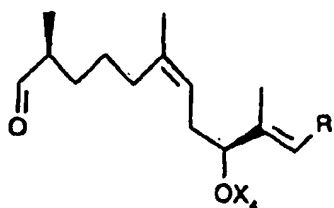
(XXIV)

worin X und X₄ jeweils für Schutzgruppen stehen und R wie bei der Formel I definiert ist, selektive Abspaltung einer Schutzgruppe von der Verbindung der Formel XXIV unter Bildung der Verbindung der Formel XXV



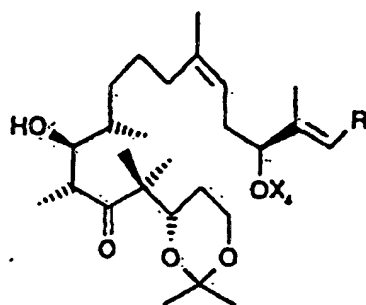
(XXV)

worin X₄ und R wie bei der Formel XXIV definiert sind, Oxidation der Verbindung der Formel XXV mit einem geeigneten Oxidans unter Bildung eines Aldehyds der Formel XXVI



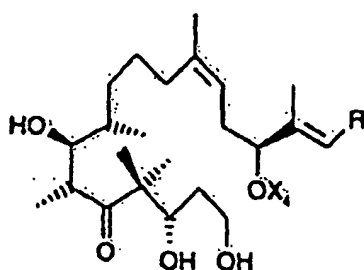
(XXVI)

worin X₄ und R wie bei der Formel XXIV definiert sind, und durch Umsetzung des dritten Zwischenprodukts der konvergenten Synthese entsprechend der Verbindung **30** mit der Verbindung der Formel XXVI in einer Aldol-Reaktion unter Bildung einer Verbindung der Formel XXVII



(XXVII)

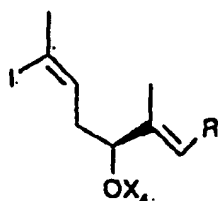
worin X_4 und R wie bei der Formel I definiert sind, Abspaltung der Schutzgruppe von der Verbindung der Formel XXVII unter Entfernung des Acetalrests und Bildung einer Verbindung der Formel XXVIII



(XXVIII)

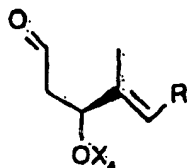
worin X_4 und R wie bei der Formel I definiert sind, und schließlich Einführung von Schutzgruppen X_1 , X_2 und X_3 mit geeigneten Reagentien unter Bildung der Verbindung der Formel I.

2. Verfahren zur Synthese einer Verbindung der Formel XX,



(XX)

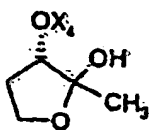
worin R für einen Heterocyclylrest steht und X_4 eine Schutzgruppe ist, gekennzeichnet durch Umsetzung einer Verbindung der Formel XIX



(XIX)

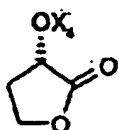
worin R und X_4 wie bei der Formel XX definiert sind, mit einer starken Base und Iod in Gegenwart von Triphenylphosphoniumiodid und anschließenden Zusatz der gleichen Base oder einer anderen starken Base wie oben unter Bildung einer Verbindung der Formel XX.

3. Verfahren zur Synthese einer Verbindung der Formel XIV



(XIV):

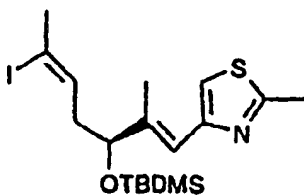
worin X_4 für eine Schutzgruppe steht, gekennzeichnet durch Umsetzung einer Verbindung der Formel XIII



(XIII)

worin X_4 für eine Schutzgruppe steht, mit einem Methylmetall oder Methylmetallderivat.

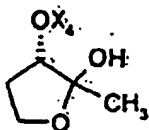
4. Verbindung der Formel



18

worin TBDMS für tert-Butyldimethylsilyl steht.

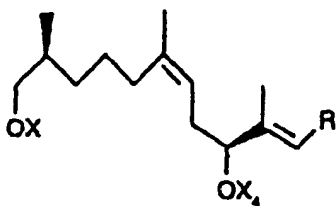
5. Verbindung der Formel XIV



(XIV).

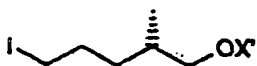
worin X_4 für eine Schutzgruppe steht, die kein tert-Butyldimethylsilyl ist.

6. Verfahren zur Synthese einer Verbindung der Formel XXIV,



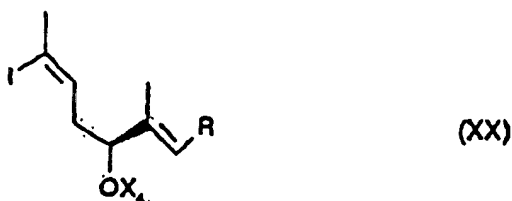
(XXIV)

worin X und X_4 für Schutzgruppen stehen und R ein Heterocyclylrest ist, gekennzeichnet durch Umsetzung einer Verbindung der Formel X



(X)

worin X' für eine Schutzgruppe steht, mit einer Suspension eines pulverförmigen Zn/Cu-Paars in Gegenwart eines Aktivators und eines Halogentrialkylsilans und **durch** anschließenden Zusatz eines Pd(0)-Komplexes in einem geeigneten Lösemittel umter Kuppelung zu einer Verbindung der Formel XX



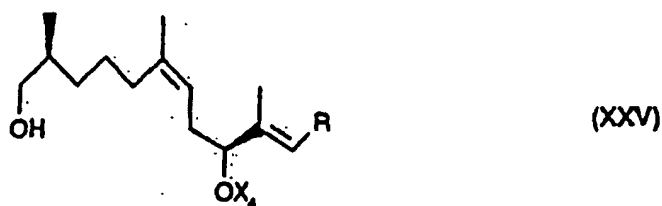
worin X₄ für eine Schutzgruppe steht und R eine Heterocyclylrest ist.

7. Verbindung der Formel XXIV



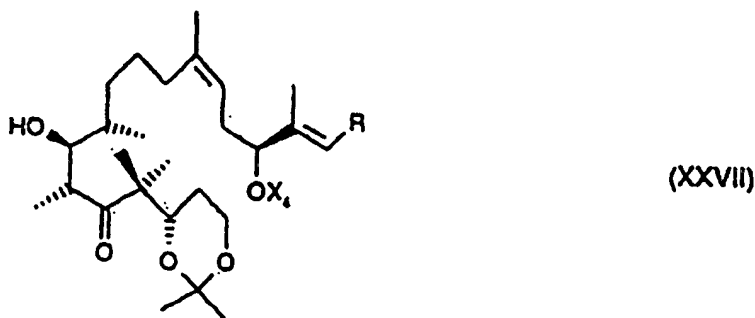
worin X und X₄ jeweils Schutzgruppen sind und R für einen Heterocyclylrest steht, in praktisch reiner cis-Form.

8. Verbindung der Formel XXV



worin X₄ eine Schutzgruppe ist und R für einen Heterocyclylrest steht, in praktische reiner cis-Form.

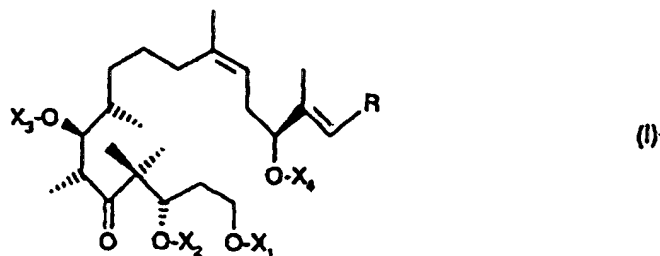
9. Verbindung der Formel XXVII



worin X₄ eine Schutzgruppe ist und R für einen Heterocyclylrest steht.

Revendications

1. Procédé de préparation d'un composé de formule I :



dans laquelle R est un groupement hétérocyclique, et X_1 , X_2 , X_3 et X_4 représentent, indépendamment l'un de l'autre, des groupes protecteurs, caractérisé en ce que :

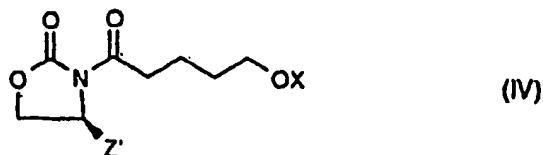
l'on amène à réagir un composé de formule II :



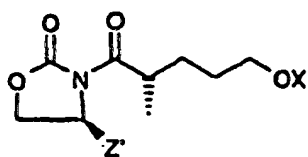
dans laquelle Y est le radical d'un acide organique ou inorganique dépourvu de son hydrogène dissociable, et X est un groupe protecteur tel que décrit ci-dessus pour X_1 à X_4 , en particulier benzyle ; avec une oxazolidone de formule III :



dans laquelle Z' est un groupe alkyle inférieur ou phényl-alkyle inférieur, dans un solvant approprié, soit (i) en présence d'une base forte, en particulier le bromure de méthylmagnésium, puis d'une base aminée tertiaire appropriée, telle que la 4-diméthylaminopyridine ; soit (ii) en présence d'un alkylure de métal alcalin ; à de faibles températures, ce qui donne un composé de formule IV :

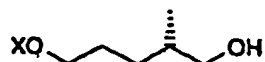


dans laquelle X et Z' ont les significations indiquées ci-dessus ; (IV) est alors C-méthylé pour donner un composé de formule V :



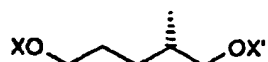
(V)

dans laquelle X et Z' sont tels que définis ci-dessus ; à partir de ce composé, puis on libère un composé de formule VI :



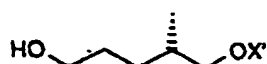
(VI)

dans laquelle X est tel qu'indiqué ci-dessus et laissé libre, par un clivage réducteur ; puis on introduit un groupe protecteur X' choisi parmi les groupes protecteurs mentionnés ci-dessus pour X₁ à X₄, mais différent de X dans la formule VI, au niveau du groupe hydroxy libre, ce qui permet que le groupe protecteur X dans le composé de formule VI puisse être éliminé par clivage sans affecter le groupe protecteur nouvellement introduit pour donner un composé à protection bis de formule VII :



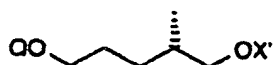
(VII)

dans laquelle X et X' sont tels que décrits ci-dessus ; à partir de ce composé, puis on élimine par clivage le groupe protecteur X dans des conditions appropriées pour donner un composé de formule VIII :



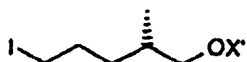
(VIII)

dans laquelle X' est tel que défini pour le composé de formule VII ; puis on amène ce composé VIII avec un halogénure d'un acide sulfonique organique pour donner l'ester d'acide sulfonique correspondant de formule IX :



(IX)

dans laquelle Q est un groupe sulfonyle organique, et on amène à réagir cet ester de sulfonyle avec un iodure métallique pour donner le composé iodure correspondant de formule X :



(X)

dans laquelle X' est tel que défini ci-dessus ; celui-ci constituant le premier de trois intermédiaires pour la synthèse convergente du composé de formule I ; en parallèle avec cette séquence de réactions,

a) on amène à réagir un composé de formule XI :



dans laquelle R est tel que décrit dans la formule I et Hal est un halogène, avec un trialkylphosphite pour donner un composé phosphonate de formule XII :



dans laquelle R est tel que défini dans la formule I, et chaque A est un groupe alkyle ;

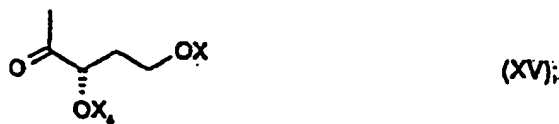
indépendamment, on amène à réagir du (5S)-(2,2-cyclohexylidène)-4-oxo-1,3-dioxolane avec un complexe $\text{BH}_3\text{-Me}_2\text{S}$ et $\text{B}(\text{OCH}_3)_3$ et du méthanol pour donner la 3(S)-dihydro-3-hydroxy-2(3H)-furanone (composé 11 dans le schéma réactionnel 2) ; qui est alors protégée par introduction d'un groupe protecteur X_4 pour donner un composé de formule XIII :



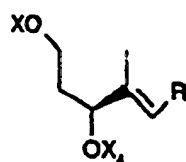
dans laquelle X_4 est un groupe protecteur ; on amène alors à réagir le composé de formule XIII avec un métal méthylique ou un dérivé de métal méthylique pour donner le composé de formule XIV :



dans laquelle X_4 est tel que défini dans la formule XIII ; on amène à réagir le composé de formule XIV avec un autre agent capable d'introduire un groupe protecteur, ce qui donne un composé de formule XV :

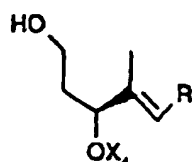


dans laquelle X et X_4 représentent un groupe protecteur, ledit composé étant amené à réagir avec un composé de phosphonate de formule XII indiquée ci-dessus en présence d'une base forte, ce qui donne un composé de formule XVII :



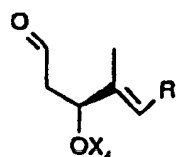
(XVII)

dans laquelle X et X₄ sont tels que définis dans la formule XIII, et R est tel que défini dans la formule I ; le composé de formule XVII étant alors partiellement déprotégé dans des conditions appropriées pour donner un composé de formule XVIII :



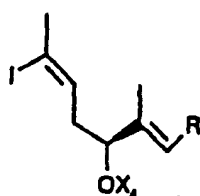
(XVIII)

dans laquelle les groupements X₄ et R sont tels que définis dans la formule XVII ; le composé de formule XVIII étant oxydé sélectivement en l'aldéhyde correspondant de formule XIX :



(XIX)

dans laquelle R et X₄ sont tels que définis dans la formule XVII, que l'on transforme alors, par réaction avec un métal alkyl-alkalin et de l'iode en présence d'iodure de triphénylphosphonium (soit avec isolement de l'iodure d'iodoéthylphosphonium ou par synthèse en une étape), et l'addition ultérieure d'une base identique ou différente de celle ci-dessus, en particulier l'hexaméthylidisilazote de sodium, en un composé de formule XX :



(XX)

dans laquelle R et X₄ sont tels que définis dans la formule XVII ; le composé de formule XX étant le deuxième des trois intermédiaires pour la synthèse convergente du composé de formule I ; le troisième intermédiaire pour la synthèse convergente étant préparé par l'un des deux procédés (a) et (b) décrits ci-après :

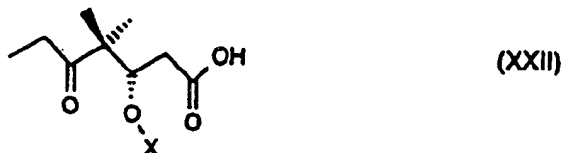
(a) une diéthylcétone est amenée à réagir, en présence de poudre de zinc activée en présence de B(OCH₃)₃, avec du 2-bromo-2-méthylpropanoate d'éthyle pour donner 2,2-diméthyl-3-éthyl-3-hydroxypentanoate d'éthyle 22, que l'on amène à réagir avec un agent déshydratant pour donner le (E)-2,2-diméthyl-2-éthyl-3-penténoate d'éthyle 23 ; que l'on amène à réagir en présence d'un hydruire complexe approprié pour donner le (E)-2,2-diméthyl-3-éthyl-3-pentén-1-ol 24 ; celui-ci est alors oxydé avec un oxydant approprié, pour donner le (E)-2,2-diméthyl-3-éthyl-3-penténal 25, que l'on amène à réagir avec de l'acétate de (S)-(-)-2-hydroxy-1,2,2-triphényle en présence d'une base forte pour donner le (3S,E)-4,4-diméthyl-5-éthyl-3-hydroxy-5-hepténoate de

(1S)-2,2,1-triphényl-2-hydroxyéthyle 26 ; on transforme ce composé, par réaction avec un hydruure complexe approprié, en le (S)-(E)-4,4-diméthyl-5-éthyl-5-heptène-1,3-diol 28, que l'on transforme alors, par réaction avec de l'acétone en présence de sulfate de cuivre anhydre, d'un acide organique fort et d'une base azotée tertiaire, pour donner le (S)-(E)-(2,2-diméthyl-[1,3]dioxan-4-yl)-3-éthyl-2-méthylpent-3-ène 29 ; on transforme alors ce composé en le troisième intermédiaire pour la synthèse convergente, l'éthylcétone (S)-2-(2,2-diméthyl-[1,3]dioxan-4-yl)-2-méthyl-pentan-3-one 30 par ozonolyse ; ou, en variante :

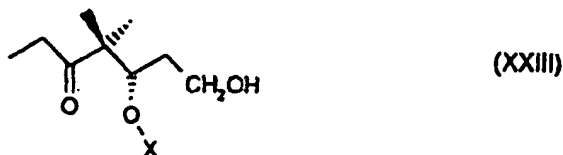
(b) le composé 30 peut être obtenu par réaction de (2R)-N-acétylbormane-10,2-sultame en présence de triflate de dialkylborane ou de chlorure de dialkylborane, et après addition d'une base azotée tertiaire, avec du 2,2-diméthyl-3-oxo-pentanal, ce qui conduit au produit sultame 31, que l'on amène alors à réagir, en présence d'une base azotée tertiaire, avec un réactif approprié à l'introduction d'un groupe protecteur pour donner un composé de formule XXI :



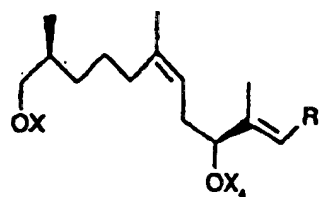
dans laquelle X est un groupe protecteur ; le composé de formule XXI est alors transformé en l'acide libre correspondant de formule XXII par réaction avec une base aqueuse appropriée :



dans laquelle X est tel que défini dans la formule XXI ; le composé de formule XXII est alors réduit en l'alcool correspondant de formule XXIII :

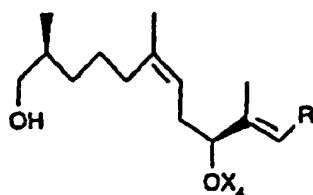


dans laquelle X est tel que défini dans la formule XXI, et finalement, ce composé est déprotégé et transformé en le composé 30 par réaction dans un mélange acétone/acide, tel qu'un mélange acétone/acide trifluoroacétique ; le composé 30 étant le troisième intermédiaire pour la synthèse convergente du composé de formule I ; et, dans une étape suivante, tout d'abord les deux intermédiaires de formules X et XX sont couplés par réaction du composé de formule X avec une suspension d'un mélange de Zn/Cu en poudre en présence d'un activateur, en présence d'halotrialkylsilane, puis par addition de palladium-tétrakis(triphénylphosphine) dans un solvant approprié, puis addition du composé de formule XX, ce qui donne un composé de formule XXIV :



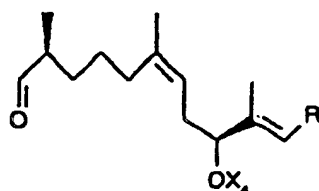
(XXIV)

dans laquelle X et X_4 représentent chacun un groupe protecteur, et R est tel que défini dans la formule I ; le composé de formule XXIV est alors déprotégé sélectivement pour donner un composé de formule XXV :



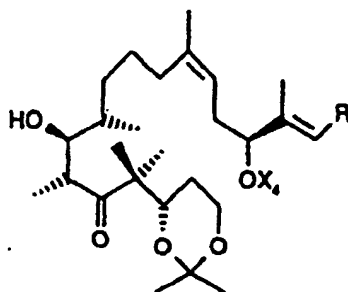
(XXV)

dans laquelle X_4 et R sont tels que définis dans la formule XXV ; le composé de formule XXV est alors oxydé avec un oxydant approprié en l'aldéhyde correspondant de formule XXVI :



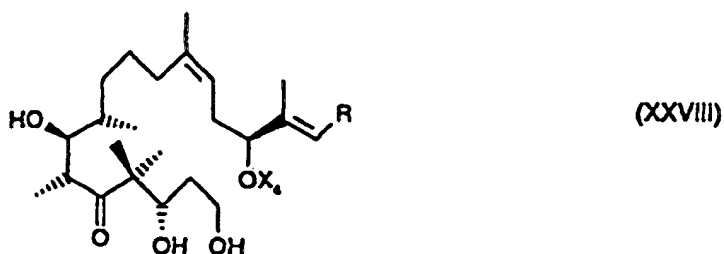
(XXVI)

dans laquelle X_4 et R sont tels que définis dans la formule XXIV ; puis le troisième intermédiaire de la synthèse convergente, le composé 30, est amené à réagir avec le composé de formule XXVI dans une réaction d'aldol, ce qui a pour résultat un composé de formule XXVII :



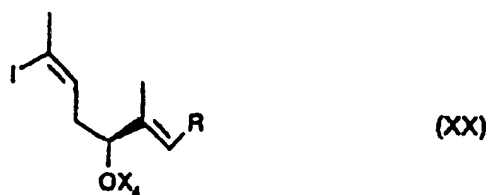
(XXVII)

dans laquelle X_4 et R sont tels que définis dans la formule I ; le composé de formule XXVII est alors déprotégé par élimination du groupement acétal, ce qui donne un composé de formule XXVIII :

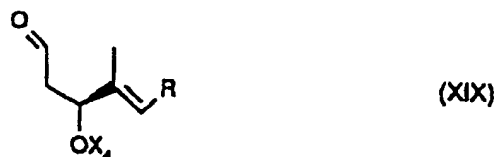


dans laquelle X_4 et R sont tels que définis dans la formule I ; et on obtient finalement le composé de formule I par introduction des groupes protecteurs X_1 , X_2 et X_3 avec des réactifs appropriés.

15 2. Procédé de synthèse d'un composé de formule XX :



dans laquelle R est un groupement hétérocyclique et X_4 est un groupe protecteur, caractérisé en ce qu'un composé de formule XIX :



dans laquelle R et X_4 sont tels que définis dans la formule XX, est transformé en un composé de formule XX par réaction avec une base forte et de l'iode en présence d'iodure de triphénylphosphonium et addition ultérieure d'une base forte identique à, ou différente de, celle indiquée ci-dessus.

40 3. Procédé de synthèse d'un composé de formule XIV :

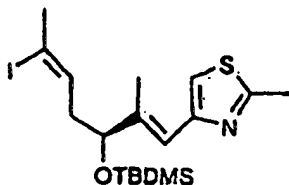


dans laquelle X_4 est un groupe protecteur, caractérisé en ce qu'un composé de formule XIII :



dans laquelle X_4 est un groupe protecteur, est amené à réagir avec un métal méthylique ou un dérivé de métal méthylique.

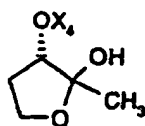
4. Composé de formule :



18

dans laquelle TBDMS est le tert-butyldiméthylsilyle.

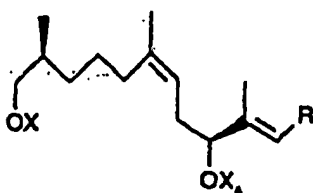
5. Composé de formule XIV :



(XIV)

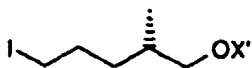
dans laquelle X_4 est un groupe protecteur différent du tert-butyldiméthylsilyle.

6. Procédé de synthèse d'un composé de formule XXIV :



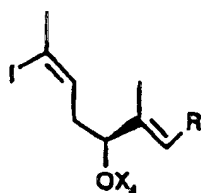
(XXIV)

dans laquelle X et X_4 représentent chacun un groupe protecteur, et R est un groupement hétérocyclique, caractérisé en ce qu'un composé de formule X :



(X)

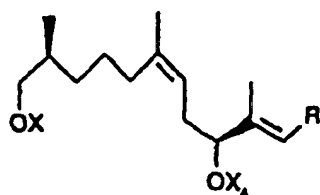
dans laquelle X' est un groupe protecteur, est couplé par réaction avec une suspension d'un mélange Zn/Cu en poudre en présence d'un activateur et d'un halotrialkylsilane, puis addition d'un complexe de Pd(0) dans un solvant approprié, avec un composé de formule XX :



(XX)

dans laquelle X_4 est un groupe protecteur et R est un groupement hétérocyclyle.

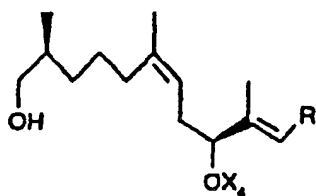
7. Composé de formule :



(XXIV)

dans laquelle X et X_4 représentent chacun un groupe protecteur, et R est un groupement hétérocyclyle, sous forme cis essentiellement pure.

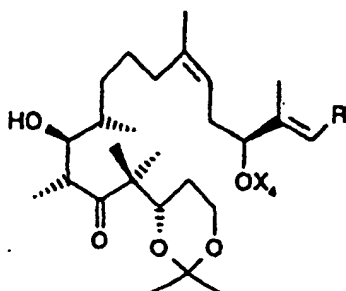
8. Composé de formule XXV :



(XXV)

dans laquelle X_4 est un groupe protecteur, et R est un groupement hétérocyclyle sous forme cis essentiellement pure.

9. Composé de formule XXVII :



(XXVII)

dans laquelle X_4 est un groupe protecteur et R est un groupement hétérocyclyle.

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